RONAN RX

PERSONALIZED MEDICINE

CLINICAL MONOGRAPH · THYROID

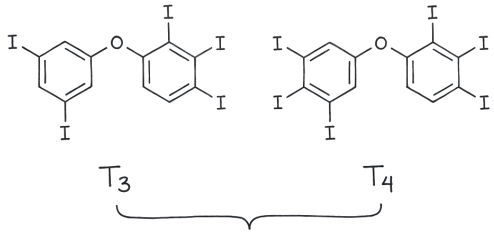
Compounded T3/T4 Combinations

Custom-ratio thyroid hormone replacement

Your thyroid gland makes two hormones: T4 (the storage form) and T3 (the active form). A healthy gland releases them in roughly a 14:1 ratio, far more T4 than T3, because the body converts T4 into T3 in tissues like the liver, brain, and muscle as needed. Standard hypothyroidism treatment in the United States is Synthroid or generic levothyroxine alone, which lets your body do the conversion itself [5][137]. Most patients feel fine on T4 alone.

Some patients still feel unwell on T4 alone, fatigue, brain fog, low mood, cold intolerance, even when their TSH lab is normal. For those patients, clinicians may consider adding a small amount of T3. The options are: (a) add Cytomel (the FDA-approved T3 tablet) to a reduced dose of levothyroxine, taken as two separate medications; (b) switch to desiccated thyroid extract (Armour, NP Thyroid, Nature-Throid), a porcine product that is FDA-approved but contains T4 and T3 in a roughly 4.2:1 ratio that doesn't match human gland output; or (c) prescribe a compounded synthetic capsule that contains both T4 and T3 at a custom ratio chosen to match human physiology (commonly 12:1 or 14:1 by weight) [2][3].

RonanRx compounds T4/T3 combination capsules under 503A only when the prescriber documents a patient-specific clinical reason, typically the need for a physiologic ratio, a sustained-release T3 component to flatten the peak that immediate-release Cytomel produces, an allergen-free formulation, or a single-capsule alternative to taking two separate tablets at offset times [5][4]. Compounded combinations are not FDA-approved and are dispensed only on a patient-specific prescription [1][5][6].



EVIDENCE POSTURE WELL STUDIED

REVIEWED **2026-05-11**

Pharmacist reviewed	Doctor led	Cold-chain ready	Patient choice preserved

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FOR CLINICIANS

Combined T4/T3 thyroid hormone replacement is a recognized but not first-line strategy for primary hypothyroidism. The 2014 ATA guideline [25], the 2012 AACE/ATA guideline [21], the 2012 ETA guideline [22], and the 2021 joint ATA/ETA/BTA consensus document [37] together endorse L-T4 monotherapy as first-line and permit a trial of combination therapy in patients with persistent symptoms despite biochemical euthyroidism on adequate monotherapy. The randomized-trial evidence base spans Bunevicius 1999 NEJM [2], Walsh 2003 JCEM [5], Clyde 2003 JAMA [6], Siegmund 2004 Clin Endocrinol (14:1 molar ratio crossover) [7], Saravanan 2005 JCEM (large community-based RCT) [8], Appelhof 2005 JCEM (two ratios) [9], Nygaard 2009 Eur J Endocrinol [13], and Shakir 2021 JCEM (three-arm crossover including desiccated thyroid extract) [38]. Meta-analyses by Grozinsky-Glasberg 2006 (eleven trials, n=1216) [11], Ma 2009 (nine trials) [15], and the Akirov 2019 individual-patient-data meta-analysis [35] do not demonstrate a consistent population-level symptom benefit, although patient preference frequently favors combination in crossover designs.

The biological rationale for combination therapy comes from preclinical work by Escobar-Morreale and colleagues showing that L-T4 monotherapy fails to normalize tissue T3 in all organs of thyroidectomized rats [44], from human cross-sectional data showing lower serum FT3 and FT3/FT4 ratio in athyreotic patients on L-T4 monotherapy versus euthyroid controls, and from the DIO2 Thr92Ala (rs225014) polymorphism reanalysis by Panicker 2009 [14] which identified homozygotes as candidate responders [18]. The Appelhof 2005 DIO2 subanalysis on a different dataset did not replicate this association [10], and no powered prospective genotype-stratified trial has confirmed the responder phenotype; population-level DIO2 genotyping is therefore not recommended [37].

Why compound rather than use desiccated thyroid extract. Pilo and colleagues' 1990 multicompartmental kinetic analysis of human thyroid hormone production [1] established that the healthy human thyroid secretes T4 and T3 in approximately a 14:1 molar ratio (equivalent to roughly 17:1 by weight using the 651 Da T4 and 651 Da T3 sodium-salt molecular weights, or 14:1 by molar quantity depending on how the ratio is normalized) [34]. Porcine-derived desiccated thyroid extract, Armour Thyroid, NP Thyroid, Nature-Throid, contains T4 and T3 in approximately a 4.2:1 ratio by weight, reflecting porcine gland physiology rather than human. The clinical implication is that DTE delivers a disproportionate T3 burden per unit T4 compared with human physiology, with each grain (60 mg) supplying roughly 38 mcg T4 and 9 mcg T3 [26]. Compounded synthetic T4/T3 capsules can be formulated at any prescribed ratio, with typical clinical practice using 12:1 to 14:1 by weight to approximate human gland output. The Siegmund 2004 trial [7] specifically tested a 14:1 molar ratio combination and reported no advantage over monotherapy on neuropsychological endpoints in unselected patients; the Hoang 2013 JCEM crossover compared DTE with L-T4 [23] and reported a patient-preference signal favoring DTE; the Shakir 2021 three-arm crossover added L-T4 + L-T3 to that comparison [38] with no clinically meaningful between-arm differences.

Pharmacokinetic considerations. Immediate-release liothyronine (Cytomel) has Tmax 2, 4 hours and produces a 30, 40% above-baseline post-dose peak in serum T3 [17], non-physiologic compared with the steady output of an intact gland. Celi 2011 used a thrice-daily dosing schedule in a JCEM crossover to flatten this peak [17]; compounded sustained-release T3 (in a combination capsule or as a separate component) is the alternative pharmacokinetic-smoothing strategy. Hennessey 2015 [26] catalogs sustained-release liothyronine and combination preparations as recognized 503A options where the immediate-release manufactured products are clinically suboptimal. The 2021 ATA/ETA/BTA consensus [37] explicitly notes that the PK profile of immediate-release liothyronine is suboptimal for steady physiologic replacement and recognizes sustained-release approaches as clinically reasonable [19].

Safety and monitoring. Combined regimens introduce a T3 component that transiently suppresses TSH after each dose; TSH-only monitoring is therefore incomplete and clinicians supplement with free T3 (ideally drawn at trough)

and free T4. Chronically suppressed TSH on long-term therapy is associated with atrial fibrillation in older adults [45][46] and with cardiovascular morbidity and fracture risk [16][47][48]. Combination regimens should not be allowed to drift into chronic TSH suppression unless suppression is the explicit therapeutic goal (e.g., post-thyroidectomy thyroid cancer protocol per the 2015 ATA differentiated-thyroid-cancer guideline [29]). T3-containing regimens are typically transitioned to L-T4 monotherapy before conception per the 2017 ATA pregnancy guideline [30][33].

Why Personalized Compounded T3/T4 Combinations

The combination-therapy trials that anchor this evidence base, Bunevicius 1999 through Shakir 2021, were powered to ask whether adding T3 helps the average hypothyroid patient. They were not powered to ask which T4:T3 ratio fits your physiology, whether you are an athyreotic patient whose remaining gland makes no T3 of its own, whether you carry the DIO2 Thr92Ala variant that may impair tissue-level conversion, or whether the post-dose serum T3 peak from immediate-release Cytomel is what is making your heart race in the afternoon. The healthy human thyroid secretes T4 and T3 in roughly a 14:1 molar ratio. Desiccated thyroid extract delivers about 4.2:1. Two off-the-shelf options at fixed ratios, and your gland output sitting somewhere they cannot reach.

That is the gap a compounding pharmacy closes. A prescriber who knows your free T3, free T4, TSH, your symptom pattern, and your tolerance for adrenergic side effects can specify a capsule at 12:1, 13:1, or 14:1 by weight, swap an immediate-release T3 component for a sustained-release T3 to flatten the Cytomel-style peak, strip the excipient you reacted to in Synthroid or Tirosint, or pair the two strengths in one capsule so you take a single pill instead of timing two tablets around food and coffee. The levothyroxine and liothyronine in the capsule are the same molecules the FDA reviewed for the single-hormone products. The ratio, the release profile, the fillers, and the strength pairing are written for you.

This is the older shape of pharmacy. A doctor who knows the patient writes the prescription. A licensed pharmacist prepares it for that named patient. State inspection, a recall path, and pharmacist review keep it honest.

Quick Facts About Compounded T3/T4 Combinations

Category: Combined thyroid hormone replacement, levothyroxine (T4) plus liothyronine (T3) at a clinician-specified ratio

Active ingredients: Levothyroxine sodium (synthetic L-thyroxine, T4) and liothyronine sodium (synthetic L-triiodothyronine, T3), each chemically identical to the endogenous hormone, combined into a single capsule at the prescribed ratio [5154]

FDA-approved comparator products: Levothyroxine (Synthroid, Levoxyl, Unithroid, Tirosint, Tirosint-SOL, AB-rated generics) and liothyronine (Cytomel, generic) are FDA-approved separately as single-hormone products. Desiccated thyroid extract (Armour Thyroid, NP Thyroid, Nature-Throid) is a fixed-ratio combination product. No FDA-approved fixed-ratio synthetic T4/T3 combination tablet is marketed in the United States. [515426]

Why compound rather than use desiccated extract: Desiccated thyroid extract (Armour, NP Thyroid, Nature-Throid) is porcine-derived and contains T4 and T3 in an approximately 4.2:1 ratio by weight, far higher in T3 than the human thyroid gland, which secretes T4 and T3 in roughly a 14:1 molar ratio per Pilo's 1990 multicompartmental kinetic analysis. Compounded synthetic T4/T3 capsules can be prepared at any prescribed ratio (commonly 12:1 to 14:1 by weight), closer to physiologic gland output, with synthetic-only ingredients and excipient control. [12623]

Evidence posture: Combination T4 + T3 therapy as a class is supported by the Bunevicius 1999 NEJM trial, multiple subsequent RCTs (Walsh 2003, Saravanan 2005, Appelhof 2005, Nygaard 2009, Siegmund 2004, Shakir 2021), the Grozinsky-Glasberg 2006 and Ma 2009 meta-analyses, the Akirov 2019 individual-patient-data meta-analysis, the 2012 ETA guidelines, the 2014 ATA guidelines, and the 2021 joint ATA/ETA/BTA consensus document. Aggregate evidence does not establish a population-level symptom advantage of combination over T4 monotherapy in unselected hypothyroid patients; patient preference frequently favors combination in crossover designs. The DIO2 Thr92Ala polymorphism (Panicker 2009) is the strongest candidate responder-phenotype signal but has not been prospectively replicated. [258913738113522253714]

FDA-approval status: Compounded T4/T3 combination capsules are not FDA-approved as a fixed-dose combination product. They are dispensed under 503A for documented patient-specific clinical needs that the individual FDA-approved single-hormone products cannot meet. [5657]

Compounded under: 503A, patient-specific prescription only

Compounded role: Documented clinical needs: (1) a custom T4:T3 ratio closer to human physiologic output (typically 12:1 to 14:1 by weight) than the 4.2:1 fixed ratio of desiccated thyroid extract; (2) sustained-release T3 component to attenuate the supraphysiologic post-dose serum T3 peak that follows immediate-release liothyronine; (3) allergen-free or excipient-substituted formulation for patients reacting to fillers in Synthroid, Cytomel, or desiccated thyroid extract; (4) custom paired strengths that simplify adherence vs taking two separate tablets at offset times [1172637]

Schedule: Not a controlled substance

Pregnancy: Hypothyroidism replacement is continued through pregnancy because untreated maternal hypothyroidism harms fetal neurodevelopment. The 2017 ATA pregnancy guideline and routine practice both transition combination T4+T3 regimens to L-T4 monotherapy before conception or in early pregnancy

because T3 does not cross the placenta as readily as T4 and is inadequate to support first-trimester fetal needs. [3025]

SPECIALS: PATIENT-SPECIFIC PRESCRIPTION ONLY

Compounded T3/T4 Combinations described in this monograph is a 503A compounded preparation. Every dose is made on a prescription, for a named patient, by a licensed pharmacist. It is not a stocked, mass-manufactured product.

- **Made to order, not off a shelf.** No batch sits in a warehouse waiting for buyers. Your prescription triggers the prep.
- **Named-patient label.** The bottle carries one patient's name. The batch records carry one prescription.
- **Dose, strength, and route chosen for the patient.** A prescriber decides what gets compounded, not a manufacturer who set the strength for a trial population.
- **Licensed pharmacist on the hook.** A real person, with a license that can be pulled, signs off on every prep. State inspectors check the facility.
- **Compounded drugs are not FDA-approved.** They should not be evaluated using branded-drug trial data alone. Availability varies by state and prescribed medication.

How This Differs from a Research-Use-Only Website

A research-use-only website ships a vial from a warehouse. There is no prescription, no pharmacist, no facility inspection, and no way to recall the product if something is wrong with it. If the vial is mislabeled, contaminated, or under-potent, there is nobody whose license is at stake.

A 503A compounding pharmacy is the other thing. The doctor writes the prescription. A licensed pharmacist, whose name is on the label, prepares the medicine in a facility the state inspects. If something goes wrong, there is a person and a license on the hook, and a documented chain of custody on every lot. That accountability is what makes it safe.

What is Compounded T3/T4 Combinations?

A compounded T4/T3 combination is a single-capsule preparation containing both levothyroxine sodium (synthetic L-T4) and liothyronine sodium (synthetic L-T3) at a clinician-specified ratio [1]. Each active ingredient is chemically identical to the endogenous hormone the human thyroid gland secretes, T4 (the storage hormone, ~7-day half-life) and T3 (the active intracellular hormone, ~24-hour half-life). The combination is compounded under 503A on a patient-specific prescription that documents the clinical reason a single-capsule custom-ratio preparation is needed in place of separately dosed Synthroid plus Cytomel, or desiccated thyroid extract.

The FDA-approved single-hormone products in the U.S [1]. are levothyroxine (Synthroid, Levoxyl, Unithroid, Tirosint, Tirosint-SOL, AB-rated generics) [5152][53] and liothyronine (Cytomel, generic; Triostat for myxedema coma) [54]. The only FDA-approved fixed-ratio combination product is desiccated thyroid extract, Armour Thyroid, NP Thyroid, and (when available) Nature-Throid, which is porcine-derived and contains T4 and

T3 in approximately a 4.2:1 weight ratio reflecting porcine gland physiology [26]. No FDA-approved fixed-ratio synthetic T4/T3 combination tablet is currently marketed in the United States; clinicians who want a synthetic combination at a physiologic ratio prescribe a compounded preparation.

Typical compounded combination capsules range from approximately 25 mcg T4 + 2 mcg T3 (12.5:1 ratio) up to 150 mcg T4 + 10 mcg T3 (15:1 ratio) per capsule. The specific strengths and ratio are individualized to the prescription. Sustained-release T3 component formulations are prepared with controlled-release excipients designed to extend T3 absorption across the dosing interval and attenuate the post-dose peak that follows immediate-release liothyronine [17][26] [1].

How Compounded T3/T4 Combinations Works

T4 is the storage hormone secreted predominantly by the thyroid gland; T3 is the biologically active intracellular hormone that occupies nuclear thyroid hormone receptors (TRα, TRβ) and drives gene transcription [26] [35]. In a healthy adult, approximately 80% of circulating T3 is generated by extrathyroidal 5'-deiodination of T4 by the iodothyronine deiodinases (DIO1, predominantly hepatic and renal; DIO2, predominantly CNS, pituitary, brown adipose tissue, skeletal muscle, placenta), and approximately 20% is secreted directly by the gland [49] [38].

Pilo and colleagues' 1990 multicompartmental kinetic analysis [1] established that the healthy human thyroid gland secretes T4 and T3 in a molar ratio of approximately 14:1, far less T3 per unit T4 than the porcine gland whose product (desiccated thyroid extract) contains T4 and T3 at roughly 4.2:1 by weight [26] [7]. This physiologic-ratio finding is the mechanistic basis for compounded synthetic T4/T3 preparations at custom ratios in the 12:1 to 14:1 range: matching the ratio of human gland output rather than the porcine ratio of DTE [9].

Combined T4/T3 replacement supplies both hormones directly, bypassing partial reliance on peripheral deiodination [26] [58]. The clinical hypothesis underpinning combination therapy is that patients with impaired T4-to-T3 conversion (DIO2 polymorphism carriers per Panicker 2009 [14], athyreotic patients with reduced glandular T3 output per Gullo 2011 [18] and Ito 2019 [33][34], or other subgroups) achieve more physiologic intracellular T3 status with a combination regimen than with L-T4 monotherapy. Whether this biochemical observation translates into a treatable symptomatic phenotype has been investigated across the combination-therapy trial literature with mixed results [21][31] [1].

Biological Role of Compounded T3/T4 Combinations

Thyroid hormone, T4 and its more active deiodination product T3, regulates basal metabolic rate, cardiac function, lipid metabolism, body temperature, central nervous system development and function, growth, and reproductive physiology across the lifespan. In adults, thyroid hormone deficiency produces hypothyroidism (fatigue, cold intolerance, weight gain, constipation, depression, bradycardia,

hyperlipidemia, anemia, in severe cases myxedema) [25]. Excess produces hyperthyroidism (palpitations, atrial fibrillation, heat intolerance, weight loss, tremor, anxiety, osteoporosis).

The healthy human thyroid gland secretes T4 and T3 in approximately a 14:1 molar ratio per Pilo and colleagues' classical multicompartmental kinetic analysis [1]. Most circulating T3 is generated by extrathyroidal deiodination of T4 by DIO1 and DIO2 [49]. The two-hormone, ratio-asymmetric output pattern is the physiologic baseline that combination thyroid hormone replacement aims to approximate when L-T4 monotherapy does not fully normalize symptomatology or peripheral T3 in selected patients [25].

Detailed Mechanism of Compounded T3/T4 Combinations

The 14:1 molar ratio rationale. Pilo and colleagues' 1990 Am J Physiol study [1] applied multicompartmental kinetic analysis to T4 and T3 turnover in human volunteers to estimate the relative thyroidal versus peripheral contributions to circulating T3. The analysis established that the healthy human thyroid gland secretes T4 and T3 in approximately a 14:1 molar ratio (translating to roughly the same 14:1 ratio by weight given the similar molecular masses of T4 and T3), substantially less T3 per unit T4 than the porcine thyroid produces. The clinical implication is that fixed-ratio porcine desiccated thyroid extract delivers a non-physiologic excess of T3 per unit T4 [23]. Compounded synthetic T4/T3 capsules at 12:1 to 14:1 by weight are designed to approximate physiologic glandular output.

The combination-therapy trial sequence. Bunevicius and colleagues' 1999 NEJM crossover trial in 33 patients [2] substituted 12.5 mcg T3 for 50 mcg T4 in standard L-T4 regimens and reported improvements in mood and neuropsychological function on the T4+T3 arm, generating the modern combination-therapy literature. Bunevicius and Prange's 2002 Endocrine follow-up in post-thyroidectomy Graves disease [3] was smaller but directionally consistent. Larger replication attempts followed and were predominantly null on primary outcomes: Walsh 2003 (n=110, 10-week crossover) [5], Clyde 2003 (n=46, 4-month parallel) [6], Siegmund 2004 (n=23, 14:1 molar ratio crossover) [7], Appelhof 2005 (n=141, two ratios) [9], Saravanan 2005 (n=697, large community-based RCT, the most adequately powered combination-therapy trial to date) [8], Nygaard 2009 (n=59 crossover) [13], and Shakir 2021 (n=75 three-arm crossover comparing L-T4, DTE, and L-T4 + L-T3) [38] [23]. The Grozinsky-Glasberg 2006 JCEM meta-analysis of eleven trials [11] and Ma 2009 meta-analysis of nine trials [15] concluded no consistent advantage on quality of life, mood, or cognitive endpoints. The Akirov 2019 individual-patient-data meta-analysis [35] reached the same overall conclusion. The Cochrane review on subclinical hypothyroidism [12] is separate from the combination-therapy question but bears on the broader replacement-therapy literature.

Patient preference signal. Several of the same trials that were null on symptom-score primary endpoints reported that patients in crossover designs preferred the combination arm [2] [23]. The Hennessey 2023 review [39] and Peterson 2018 online survey of hypothyroid patients [32] document a persistent patient-side dissatisfaction signal on L-T4 monotherapy that does not align neatly with trial-level objective endpoints, interpreted variously as a placebo or expectancy effect, a small genuine effect not captured by standardized

symptom instruments, or a genuine responder phenotype masked by averaging across unselected populations.

The DIO2 polymorphism candidate-moderator hypothesis [23]. The DIO2 Thr92Ala (rs225014) polymorphism is a common variant in the DIO2 gene with allele frequency approximately 30, 40% in populations of European ancestry. Panicker and colleagues 2009 JCEM [14] reanalyzed the Saravanan/ Bunevicius combined-therapy datasets and reported that homozygotes for the Ala allele had lower baseline psychological well-being on T4 monotherapy and reported greater symptomatic improvement from combination therapy than non-carriers. The Appelhof 2005 DIO2 subanalysis on a different dataset and outcome panel did not replicate the association [10]. The candidate-moderator hypothesis is biologically plausible, Ala/Ala homozygotes have reduced DIO2 catalytic activity and would be expected to generate less local T3 in DIO2-expressing tissues, but has not been prospectively replicated in a powered genotype-stratified trial. Population-level DIO2 genotyping is not recommended by the 2014 ATA [25], 2012 ETA [22], or 2021 joint consensus [37].

Athyreotic patients as a subgroup. Gullo and colleagues' 2011 PLoS One cross-sectional analysis (n=1811 athyreotic, n=3875 controls) [18] demonstrated lower FT3 and FT3/FT4 ratio in L-T4-monotherapy-treated patients without a thyroid gland compared with euthyroid controls at any given TSH, biochemical evidence that L-T4 alone does not fully normalize peripheral T3 status in this subgroup [26]. Ito and colleagues confirmed this in post-radioiodine Graves disease [34] and post-thyroidectomy populations with residual hypothyroid symptoms despite TSH in reference range [33]. Gullo 2017 documented seasonal TSH variation in this cohort [19]. McAninch and Bianco 2015 Lancet Diabetes Endocrinol [28] and Ettleson and Bianco 2020 JCEM [36] integrate these strands into a clinical case for individualized trial of combination therapy in athyreotic patients with persistent symptoms.

Pharmacokinetic considerations for the T3 component. Native circulating T3 has a serum half-life of approximately 1 day. Oral immediate-release liothyronine produces a Tmax of 2, 4 hours and a 30, 40% above-baseline post-dose peak [17]. Celi and colleagues used a thrice-daily dosing schedule in their JCEM crossover trial to flatten this peak and reported comparable TSH suppression with improvement in lipid panel and modest weight reduction on the T3 arm vs equivalent-dose L-T4 [17 23]. Compounded sustained-release T3, formulated with hydrophilic-matrix or coated-bead excipients to extend absorption across 8, 24 hours, is the alternative pharmacokinetic-flattening approach and is well-suited to incorporation in a single-capsule T4/T3 combination. The 2021 ATA/ETA/BTA consensus document [37] explicitly acknowledges the suboptimal PK of immediate-release liothyronine and recognizes sustained-release preparations as a clinically reasonable approach.

HPT axis monitoring under combination therapy [23]. Hoermann and colleagues' 2015 Frontiers in Endocrinology modeling work [27] characterized the HPT-axis homeostatic deviations on L-T4 monotherapy and noted that TSH-only targeting leaves a meaningful subset of patients with discordant FT3 status. Under combination therapy, the post-dose T3 peak from any immediate-release T3 component further degrades the reliability of TSH-only monitoring; supplementing with FT3 (trough draw) and FT4 measurements is standard [37 27].

Compounded T3/T4 Combinations Research History

Thyroid hormone replacement traces to the 1890s, when George Murray demonstrated that injectable sheep-thyroid extract reversed myxedema. For roughly the first half of the twentieth century, porcine desiccated thyroid extract, Armour Thyroid (introduced 1899), later supplemented by Nature-Throid and NP Thyroid, was the dominant clinical preparation [26][31]. Synthetic levothyroxine became commercially available in the 1950s, and Cytomel (synthetic liothyronine, T3) was FDA-approved in 1956. By the 1970s, levothyroxine monotherapy had largely displaced desiccated extract as standard care, supported by the recognition that T4's long half-life produced more reproducible serum levels and that peripheral deiodination would supply tissue T3 [31].

The modern combination-therapy debate began with Bunevicius and colleagues' 1999 NEJM crossover trial [2], which reported mood and cognitive benefit from partial T4-to-T3 substitution and reopened the question of whether L-T4 monotherapy is sufficient for all patients. A series of larger replication trials followed, Walsh 2003 [5], Clyde 2003 [6], Siegmund 2004 (a 14:1 molar ratio combination crossover testing the physiologic-ratio hypothesis directly) [7], Saravanan 2005 (the largest combination-therapy trial conducted, n=697 community-based RCT) [8], Appelhof 2005 (two ratios) [9], Nygaard 2009 [13], and Shakir 2021 (three-arm crossover comparing L-T4, desiccated thyroid extract, and L-T4 + L-T3) [38]. Meta-analyses by Grozinsky-Glasberg 2006 [11], Ma 2009 [15], and the Akirov 2019 individual-patient-data analysis [35] consolidated the conclusion that combination therapy does not produce a consistent population-level advantage on symptom or quality-of-life endpoints, although patient preference frequently favored combination in crossover designs.

Mechanistic interest in a responder phenotype emerged with the Panicker 2009 JCEM reanalysis of the Saravanan and Bunevicius datasets [14], which identified the DIO2 Thr92Ala polymorphism as a candidate moderator. The Appelhof 2005 DIO2 subanalysis on a different dataset did not replicate the association [10]. The athyreotic-subgroup hypothesis was advanced by Gullo and colleagues' 2011 PLoS One cross-sectional analysis [18] showing measurably lower FT3 and FT3/FT4 ratio in athyreotic L-T4-monotherapy-treated patients versus euthyroid controls, with Ito and colleagues' 2019 follow-up work confirming the pattern in post-thyroidectomy and post-radioiodine populations and linking it to residual symptoms [33][34]. McAninch and Bianco's 2015 Lancet Diabetes Endocrinol review [28] and Ettleson and Bianco's 2020 JCEM review [36] integrated these strands into a clinical case for individualized trial of combination therapy in selected patients.

Desiccated thyroid extract returned to clinical attention with the Hoang 2013 JCEM randomized crossover [23] comparing DTE with L-T4 in primary hypothyroidism, which reported no mean difference in symptom or neuropsychological scores but a patient-preference signal favoring DTE in 48.6% of participants. The Shakir 2021 three-arm crossover [38] added an L-T4 + L-T3 arm to that comparison and reported no clinically meaningful between-arm differences with patient preferences distributed across the three

regimens. The Hennessey 2023 review [39] surveyed the L-T4 monotherapy literature and unmet-need evidence; the Peterson 2018 online survey of hypothyroid patients [32] documented a persistent dissatisfaction signal on L-T4 monotherapy.

Guideline consolidation. The 2012 AACE/ATA guideline [21] and the 2014 ATA guideline [25] endorsed L-T4 monotherapy as first-line and did not routinely recommend combination therapy, while permitting a trial in selected patients. The 2012 ETA guideline [22] was more permissive of trial use of combination therapy in symptomatic patients. The 2021 joint ATA/ETA/BTA consensus document [37] codified an individualized, conditional approach, permitting a trial of combination therapy with pre-specified endpoints and trial duration, recognizing sustained-release liothyronine as a reasonable formulation approach, and declining to recommend population-level DIO2 genotyping in the absence of replicated prospective trial data. Compounded synthetic T4/T3 combination capsules at physiologic ratios are the practical 503A vehicle through which a substantial fraction of combination-therapy prescriptions are filled, even though no FDA-approved fixed-ratio synthetic combination tablet is marketed in the United States.

Compounded T3/T4 Combinations Timeline

1891 • George Murray demonstrates injectable sheep-thyroid extract reverses myxedema, first effective thyroid hormone replacement

1899 • Armour & Co [26]. introduces commercial porcine desiccated thyroid extract (Armour Thyroid)

1950s • Synthetic levothyroxine (L-T4) enters clinical practice and progressively replaces desiccated thyroid extract as standard hypothyroidism therapy [31]

1956 • FDA approves Cytomel (liothyronine sodium tablets, 5/25/50 mcg) [54]

1990 • Pilo et al [1]. (Am J Physiol) publish multicompartmental kinetic analysis establishing the human thyroid secretes T4 and T3 in approximately a 14:1 molar ratio, physiologic-ratio rationale for synthetic T4/T3 combinations

1995 • Escobar-Morreale et al [44]. (J Clin Invest) demonstrate in thyroidectomized rats that L-T4 monotherapy fails to normalize tissue T3 in all organs, preclinical foundation for combination-therapy interest

1999 • Bunevicius et al [2]. (NEJM) publish landmark 33-patient crossover showing mood and cognitive benefit from partial T4-to-T3 substitution, re-opens the combination-therapy question

2002 • Bunevicius & Prange (Endocrine) repeat the comparison in post-thyroidectomy Graves disease patients; Saravanan et al [34]. (Clin Endocrinol) report community-wide L-T4-monotherapy well-being deficit

2003 • Walsh et al [5]. (JCEM) and Clyde et al [6]. (JAMA) publish larger combination-therapy trials with predominantly null primary outcomes

2004 • Siegmund et al [7]. (Clin Endocrinol) test a 14:1 molar ratio L-T4 + L-T3 combination crossover, null primary endpoint, but the trial directly addresses the physiologic-ratio hypothesis

2004 • Sawin (Thyroid) and Surks (JAMA AACE/ATA/Endocrine Society consensus) catalog atrial-fibrillation and cardiovascular risk of subclinical hyperthyroidism, relevant to T3-component dosing [45][46]

2005 • Saravanan et al. (JCEM) publish the largest combination-therapy RCT to date (n=697 community-based), null primary outcome; Appelhof et al [8][9][10]. (JCEM) compare two T4:T3 dose ratios, null primary outcome; companion DIO2 polymorphism subanalysis (Appelhof) also null

2006 • Grozinsky-Glasberg et al [11]. (JCEM) meta-analyze 11 combination-therapy trials (n=1216), no consistent advantage on quality of life or mood

2007 • Cochrane review (Villar et al.) on thyroid hormone replacement for subclinical hypothyroidism, context for the broader replacement-therapy evidence base [12]

2008 • Biondi & Cooper (Endocr Rev) publish authoritative review of subclinical thyroid dysfunction including the cardiovascular and skeletal implications of suppressed TSH [4][7]

2009 • Panicker et al. (JCEM) reanalyze the Saravanan/Bunevicius datasets and identify DIO2 Thr92Ala polymorphism as a candidate moderator; Ma et al [14]. (Nucl Med Commun) and Nygaard et al [15][13]. (Eur J Endocrinol) add to the meta-analytic and trial dataset

2010 • Flynn et al [16]. (JCEM) link suppressed serum TSH in long-term thyroxine-treated patients to cardiovascular morbidity and fractures

2011 • Celi et al. (JCEM) thrice-daily L-T3 vs L-T4 crossover, comparable TSH suppression, improvement in lipid markers on L-T3 arm; Gullo et al [17][18]. (PLoS One) show athyreotic patients on L-T4 monotherapy have lower FT3 and FT3/FT4 ratio than euthyroid controls

2012 • AACE/ATA guideline (Garber et al.) and ETA guideline (Wiersinga et al.) on hypothyroidism management; Biondi & Wartofsky (JCEM) review combination treatment, toward personalized replacement [2][12][20]

2013 • Hoang et al [23][24]. (JCEM) randomized crossover compares desiccated thyroid extract with L-T4, patient preference favored DTE (48.6%); ETA subclinical hypothyroidism guideline (Pearce et al.) published

2014 • Jonklaas et al [25]. publish 2014 American Thyroid Association guidelines on hypothyroidism treatment, L-T4 monotherapy first-line; combination therapy not routinely recommended but trial permitted in selected patients

2015 • Hennessey (Endocr Pract) historical and current perspective on thyroid extract; Hoermann et al [262728]. (Front Endocrinol) model HPT axis homeostasis under monotherapy; McAninch & Bianco (Lancet Diabetes Endocrinol) review variable effectiveness of L-T4 monotherapy

2017 • ATA pregnancy guideline (Alexander et al.) addresses thyroid hormone replacement during pregnancy; Hennessey (Endocrine) reviews emergence of levothyroxine as standard therapy [3031]

2018 • Peterson et al [3250]. (Thyroid) online survey of hypothyroid patients documents prominent dissatisfaction on L-T4 monotherapy; Dayan & Panicker (Thyroid Res) practical-implementation review of combination therapy

2019 • Ito et al. (Thyroid; Endocr J) report low serum FT3 and residual hypothyroid symptoms in athyreotic L-T4-monotherapy-treated patients; Akirov et al [333435]. (Front Endocrinol) individual-patient-data meta-analysis of combination therapy

2020 • Ettleson & Bianco (JCEM) review individualized therapy for hypothyroidism and the case for a combination-therapy trial in selected patients [36]

2021 • Jonklaas, Bianco, Cappola et al. publish joint ATA / ETA / BTA consensus document on the evidence-based use of L-T4/L-T3 combinations; Shakir et al [3738]. (JCEM) three-arm crossover comparison of L-T4, DTE, and L-T4 + L-T3

2023 • Hennessey (Endocr Pract), what works better for the individual with hypothyroidism (L-T4 monotherapy and alternatives) [39]

Clinical Contexts for Compounded T3/T4 Combinations

Primary hypothyroidism, combination T4 + T3 therapy in patients with persistent symptoms despite L-T4 monotherapy WELL STUDIED

Studied in the combination-therapy trial sequence and supported as a conditional individualized option by the 2012 ETA, 2014 ATA, and 2021 joint ATA/ETA/BTA consensus documents. Not first-line. No FDA-approved fixed-ratio synthetic combination product; combination is achieved with separate FDA-approved tablets, with desiccated thyroid extract, or with a 503A compounded synthetic combination capsule.

Combination T4 + T3 therapy is the recognized approach for hypothyroid patients with persistent symptoms despite biochemical euthyroidism on adequate L-T4 monotherapy [8,9,13]. The trial-level evidence base [2] is mixed-to-null on objective primary endpoints; the Grozinsky-Glasberg 2006, Ma 2009, and Akirov 2019 meta-analyses confirm no consistent population-level benefit [6,35]. Patient preference frequently favors combination in crossover designs [3,8,11,15]. The 2012 ETA [22], 2014 ATA [25], and 2021 joint ATA/ETA/BTA consensus [37] all endorse a conditional trial in selected patients. Compounded synthetic combination at a physiologic 12:1 to 14:1 ratio approximates human gland output per Pilo 1990 [1] more closely than the 4.2:1 ratio of porcine desiccated thyroid extract [26]; the Siegmund 2004 trial [7] specifically tested a 14:1 ratio and was null on primary endpoint but did not directly test the desiccated-extract comparison. Sustained-release T3 incorporated into a compounded combination addresses the supraphysiologic peak that immediate-release liothyronine produces [17,37,5].

Athyreotic patients with persistent symptoms despite TSH-targeted L-T4 monotherapy WELL STUDIED

A defined subgroup with biochemical evidence (lower FT3, lower FT3/FT4 ratio) that L-T4 monotherapy may be incompletely normalizing peripheral T3 status; combination therapy is more often considered in this subgroup than in unselected hypothyroid populations.

Athyreotic patients, post-thyroidectomy or post-radioiodine, have measurably lower FT3 and FT3/FT4 ratio on L-T4 monotherapy than euthyroid controls at any given TSH per the Gullo 2011 PLoS One cross-sectional analysis (n=1811 athyreotic vs 3875 controls) [18], confirmed by Ito 2019 in post-radioiodine Graves [34] and post-thyroidectomy populations with residual symptoms despite TSH in reference range [33]. The McAninch and Bianco 2015 review [28] and Ettleson and Bianco 2020 review [36] frame this as the most defensible patient subgroup for a clinical trial of combination therapy [37]. Compounded synthetic T4/T3 capsules at a physiologic ratio are a practical vehicle for such trials [19].

DIO2 Thr92Ala polymorphism carriers, candidate responder phenotype EMERGING

Hypothesis-generating signal from the Panicker 2009 reanalysis; not prospectively replicated; population genotyping not recommended.

Panicker and colleagues' 2009 JCEM reanalysis of the Saravanan/Bunevicius datasets [14] identified DIO2 Thr92Ala (rs225014) homozygotes as having lower baseline psychological well-being on L-T4 monotherapy and reporting greater symptomatic benefit from combination therapy than non-carriers. The Appelhof 2005 DIO2 subanalysis on a different dataset did not replicate this finding [10]. The candidate-moderator hypothesis is biologically plausible, Ala homozygotes have reduced DIO2 catalytic activity and less local T3 generation in DIO2-expressing tissues, but has not been prospectively replicated in a powered genotype-stratified trial. The 2014 ATA [25], 2012 ETA [22], and 2021 joint consensus [37] do not recommend population genotyping.

Switch from desiccated thyroid extract to a physiologic-ratio synthetic combination

WELL STUDIED

Pragmatic indication when a patient is currently on Armour Thyroid, NP Thyroid, or Nature-Throid and the clinician wants to move toward a physiologic T4:T3 ratio with synthetic-only ingredients.

Desiccated thyroid extract contains T4 and T3 in approximately a 4.2:1 weight ratio reflecting porcine gland physiology [26], substantially different from the 14:1 human glandular ratio established by Pilo 1990 [1]. The Hoang 2013 JCEM crossover [23] reported patient preference favoring DTE over L-T4 in 48.6% of participants without a mean symptom-score difference. The Shakir 2021 three-arm crossover [38] added an L-T4 + L-T3 arm and reported no clinically meaningful differences. A compounded synthetic T4/T3 capsule at a 12:1 to 14:1 ratio is the bridge formulation when a clinician wants to retain a multi-hormone replacement strategy while moving toward a more physiologic ratio and synthetic-only ingredients (eliminating porcine-derived material and the variable T3 content sometimes reported with desiccated extract).

Off-Label Uses of Compounded T3/T4 Combinations

T3-component augmentation in major depressive disorder, delivered as a combination capsule with L-T4 EMERGING

*Off-label; the T3 augmentation evidence base is from Joffe 1993, Aronson 1996, Cooper-Kazaz 2007, and STAR*D level 3, all of which used liothyronine alone added to antidepressant therapy. Combination T4/T3 capsules are not directly studied for this indication.*

T3 augmentation in major depressive disorder partially or unresponsive to standard antidepressants is supported by trial-level evidence using stand-alone liothyronine [40][42]. Delivering the T3 augmentation as part of a compounded T4/T3 combination is a formulation choice rather than a separately studied indication; the underlying evidence applies to the T3 component, and the T4 component supplies maintenance thyroid hormone for any concurrent hypothyroidism [41][43].

Compounded Compounded T3/T4 Combinations (503A)

Compounded synthetic T4/T3 combination capsules occupy a specific 503A niche because no FDA-approved fixed-ratio synthetic combination product is marketed in the United States [5][6]. The FDA-approved single-hormone products are levothyroxine (Synthroid, Levoxyl, Unithroid, Tirosint, Tirosint-SOL, AB-rated generics) [51][52][53] and liothyronine (Cytomel, generic; Triostat for myxedema coma) [54]. The only FDA-approved fixed-ratio combination is porcine desiccated thyroid extract, Armour Thyroid, NP Thyroid, and (when available) Nature-Throid, at approximately a 4.2:1 T4:T3 weight ratio [26]. A clinician who wants a synthetic combination at a physiologic 12:1 to 14:1 ratio per Pilo 1990 [1] must either prescribe both tablets separately or use a 503A compounded combination capsule.

Four documented patient-specific clinical needs drive most compounded T4/T3 combination prescriptions. (1) Physiologic ratio: a 12:1 to 14:1 weight ratio closer to human glandular output than the 4.2:1 ratio of desiccated thyroid extract, with synthetic-only ingredients and no porcine-derived material. (2) Sustained-release T3 component: incorporation of a controlled-release T3 fraction to attenuate the supraphysiologic post-dose peak that immediate-release liothyronine produces [17][37][9]. (3) Allergen-free or excipient-substituted formulation: avoidance of lactose, modified food starch, calcium sulfate, dyes, or other excipients present in Synthroid, Cytomel, or desiccated thyroid extract to which the patient has documented sensitivity [5][6][38]. (4) Single-capsule simplification: a single combination capsule in place of two separate tablets (commonly L-T4 in the morning fasting and L-T3 either at the same time or split across the day), improving adherence in patients for whom the two-tablet regimen is failing on practical grounds [13].

Outside these patient-specific clinical needs, compounding of T4/T3 combinations is not appropriate under 503A. Routine substitution of a compounded synthetic combination for separately dosed FDA-approved

tablets without a documented clinical reason does not meet the patient-specific clinical need threshold under FDA's essentially-a-copy framework [57]. RonanRx does not fill compounded T4/T3 combination prescriptions on a preference- or price-only basis. Levothyroxine is also classified by FDA as a narrow-therapeutic-index drug with bioequivalence considerations that elevate the importance of consistent formulation and dosing in any patient on chronic therapy [55]; the compounded combination batch documentation reflects this status [56 8].

Evidence-base note: compounded synthetic T4/T3 combination capsules at physiologic ratios are not directly tested as a category in randomized controlled trials [56 56]. The combination-therapy trial sequence [2] used separately dosed L-T4 and L-T3 tablets at various ratios. The Siegmund 2004 trial [7] is the closest direct test of a 14:1 ratio, null on primary endpoint, consistent with the broader combination-therapy literature. The compounded use case is therefore an extrapolation of the combination-therapy evidence base applied through a formulation (single-capsule physiologic-ratio synthetic) that the published trials did not directly study.

Compounded T3/T4 Combinations Formulations and Routes

Form	Concentration	Description
Compounded synthetic T4/T3 combination capsule, immediate-release T3 component	Custom, typical strengths in the range of 25 mcg T4 + 2 mcg T3 (12.5:1) up to 150 mcg T4 + 10 mcg T3 (15:1) per capsule	Single-capsule combination of levothyroxine sodium USP and liothyronine sodium USP at a prescribed T4:T3 weight ratio (commonly 12:1 to 14:1). The T3 component is immediate-release. Used when the clinical priority is a physiologic ratio in a single capsule. [12637]
Compounded synthetic T4/T3 combination capsule, sustained-release T3 component	Custom, typical strengths similar to immediate-release combinations	Capsule combining immediate-release T4 with a controlled-release T3 fraction prepared with hydrophilic-matrix or coated-bead excipients to extend T3 absorption across 8, 24 hours and attenuate the supraphysiologic peak that follows immediate-release liothyronine. Stability and release profile are documented per the pharmacy's product-specific data. [172637]
Compounded allergen-free or excipient-substituted T4/T3 combination capsule	Matches the prescribed dose at the prescribed ratio	Combination capsule prepared without lactose, corn-derived starch, gluten-cross-contaminated excipients, dyes, or other excipients to which the patient has documented sensitivity. [5154]
Manufactured desiccated thyroid extract (reference combination product)	1 grain (60 mg) ≈ 38 mcg T4 + 9 mcg T3 (4.2:1 weight ratio); strengths 15, 30, 60, 90, 120 mg	Porcine desiccated thyroid USP, Armour Thyroid, NP Thyroid, Nature-Throid. FDA-approved fixed-ratio combination product. Ratio reflects porcine gland

Form	Concentration	Description
		physiology and is not matched to the human 14:1 molar ratio established by Pilo 1990. [26123]
Manufactured levothyroxine and liothyronine taken as two separate tablets	L-T4 (Synthroid 25, 300 mcg; Tirosint capsule 13, 200 mcg; Tirosint-SOL solution 13, 200 mcg) plus L-T3 (Cytomel 5/25/50 mcg)	FDA-approved single-hormone tablets prescribed together. The two-tablet regimen achieves combination therapy without compounded preparation but requires the patient to manage two prescriptions and (often) offset dosing times. [51525354]

Routes used in published literature: oral.

Compounded T3/T4 Combinations Dosing

Route	Population	Range	Duration	Study type
Oral (compounded synthetic T4/T3 combination capsule)	Adults on L-T4 monotherapy with persistent symptoms despite biochemical euthyroidism, considered for a combination-therapy trial per the 2021 ATA/ETA/BTA consensus	Initial dose individualized to the patient's current L-T4 maintenance dose and clinical context. Typical practice: replace the L-T4 monotherapy dose with a combination capsule that supplies approximately the same total daily T4 plus a small T3 component at a 12:1 to 14:1 weight ratio (e.g., a patient on 112 mcg L-T4 daily may transition to a combination capsule supplying 100 mcg T4 + 7.5 mcg T3, approximately 13:1 by weight).	Trial period of 3, 6 months with pre-specified symptom and laboratory endpoints; continue only if clear symptomatic benefit per the 2021 consensus document	Joint ATA/ETA/BTA consensus document; combination-therapy trial regimens (Bunevicius 1999, Walsh 2003, Siegmund 2004, Saravanan 2005, Appelhof 2005, Nygaard 2009, Shakir 2021)
Oral (combination via separately dosed FDA-approved tablets)	Adults on L-T4 monotherapy with persistent symptoms; clinician prefers FDA-approved single-hormone products	Reduce L-T4 by approximately 50 mcg and add 5, 12.5 mcg L-T3 (Cytomel or generic liothyronine) daily, targeting an L-T4:L-T3 weight ratio in the 13:1 to 20:1 range per the 2021 consensus document.	Trial period of 3, 6 months	Joint ATA/ETA/BTA consensus document; published combination-therapy trial regimens

Route	Population	Range	Duration	Study type
		Reassess TSH, FT4, and trough FT3 at 6, 8 weeks.		
Oral (desiccated thyroid extract, comparator regimen)	Adults with primary hypothyroidism; patient or clinician preference for a porcine fixed-ratio combination	Typical conversion: 1 grain (60 mg) of desiccated thyroid extract is approximately equivalent to 100 mcg of L-T4 in terms of T4 content but additionally supplies approximately 9 mcg T3 per grain (4.2:1 ratio). Titrated by TSH and clinical response.	Indefinite while clinically beneficial	FDA-approved labeled regimen; Hoang 2013 crossover; Shakir 2021 three-arm crossover

Doses listed reflect published combination-therapy trial regimens and the 2021 ATA/ETA/BTA consensus document. They are not RonanRx prescribing recommendations. The prescribing clinician selects the formulation, T4:T3 ratio, and total dose based on the patient's clinical context, etiology of hypothyroidism (autoimmune, athyreotic post-thyroidectomy or post-radioiodine, central), age, cardiovascular status, prior tolerability of immediate-release Cytomel, prior tolerability of desiccated thyroid extract, and the explicit therapeutic goal of the combination trial.

Combination therapy is not first-line. The 2012 AACE/ATA [21] and 2014 ATA [25] guidelines recommend L-T4 monotherapy as preferred replacement; the 2012 ETA [22] and 2021 joint consensus [37] permit a conditional trial of combination therapy in patients with persistent symptoms on adequate L-T4 monotherapy. A reasonable trial structure is 3, 6 months with pre-specified symptom and laboratory endpoints; therapy is continued only if a clear symptomatic benefit is documented and verified after re-checking TSH-targeted L-T4 monotherapy.

When immediate-release liothyronine is the T3 component, the post-dose peak can produce transient adrenergic symptoms; dividing the daily dose (twice or thrice daily) attenuates this peak [17]. A compounded sustained-release T3 component or sustained-release combination capsule is the alternative pharmacokinetic-smoothing strategy [2637]. Cardiac-disease and elderly patients should start at lower total doses with slow titration; chronically suppressed TSH on long-term therapy is associated with atrial fibrillation and fracture risk [164645].

Pregnancy. Combination T4+T3 regimens are typically transitioned to L-T4 monotherapy before conception or in early pregnancy because T3 does not cross the placenta as readily as T4 and is inadequate to support first-trimester fetal needs per the 2017 ATA pregnancy guideline [30].

Switching from desiccated thyroid extract. When transitioning a patient from DTE to a compounded synthetic combination, total T4 and T3 content should be approximately matched on a milligram basis (1

grain ≈ 38 mcg T4 + 9 mcg T3) and then re-titrated by TSH, FT4, and trough FT3 over 6, 12 weeks per clinical response.

Compounded T3/T4 Combinations Safety

Combined T4/T3 thyroid hormone safety at replacement doses is dominated by signs and symptoms of relative hyperthyroidism if dosing exceeds physiologic requirement: palpitations, tachycardia, atrial fibrillation, tremor, heat intolerance, weight loss, anxiety, insomnia, diarrhea, menstrual irregularity, and accelerated bone resorption. The T3 component is the principal driver of post-dose adrenergic symptoms because immediate-release liothyronine produces a supraphysiologic peak in serum T3 [17]. Compounded sustained-release T3 in a combination capsule attenuates this peak and is the principal pharmacokinetic argument for the compounded preparation over a two-tablet regimen using immediate-release Cytomel.

Cardiovascular safety is the principal organ-system concern. Long-term suppressed serum TSH in thyroid-hormone-treated patients is associated with atrial fibrillation [4546] and increased cardiovascular morbidity and fracture risk [16]. Biondi and Klein (2004) reviewed the cardiovascular consequences of subclinical hyperthyroidism [48]; Biondi and Cooper (2008) reviewed the broader subclinical-dysfunction literature [47]. Combination regimens should not be allowed to drift into chronic TSH suppression unless TSH suppression is the explicit goal of therapy (e.g., post-thyroidectomy thyroid cancer protocol per the 2015 ATA differentiated-thyroid-cancer guideline [29]). Patients with established ischemic heart disease should start at the lowest effective dose with slow titration.

Bone health is affected by chronic over-replacement: suppressed TSH and elevated FT3 accelerate bone turnover and are associated with reduced bone mineral density and increased fracture risk in postmenopausal women and older men [1647]. Bone health monitoring is reasonable when TSH is chronically suppressed.

Allergen and excipient considerations. Synthroid, Cytomel, and desiccated thyroid extract each contain different excipients (lactose, modified food starch, calcium sulfate, povidone, dyes); compounded combination capsules can be prepared without the offending excipient when the patient has a documented sensitivity. Levothyroxine is classified by FDA as a narrow-therapeutic-index drug [55], and consistent formulation is a clinically meaningful consideration on chronic therapy.

Compounded synthetic T4/T3 combination capsules are not FDA-approved and have not undergone the bioavailability, content-uniformity, and labeling review that the manufactured single-hormone products have. Compounded sustained-release T3 in particular has a release profile that depends on the formulation excipients and process; documented stability data, content-uniformity testing, and product-specific pharmacist review are essential before dispensing. Pregnancy is a context in which combination T4+T3 regimens are typically transitioned to L-T4 monotherapy [30].

Contraindications

Combined T4/T3 thyroid hormone is contraindicated in: uncorrected adrenal insufficiency (thyroid hormone increases tissue demand for cortisol and can precipitate adrenal crisis if cortisol replacement is not in place); untreated thyrotoxicosis; and acute myocardial infarction (relative, short-term avoidance until clinically stable) [25]. Hypersensitivity to levothyroxine sodium, liothyronine sodium, or to a tablet/capsule excipient is also a contraindication for the affected product.

Caution is required in: cardiovascular disease (ischemic heart disease, arrhythmia, untreated hypertension); elderly patients (start at the lowest effective total dose); diabetes mellitus (may increase insulin or oral hypoglycemic requirements as hypothyroidism resolves); and patients receiving anticoagulants (thyroid hormone potentiates warfarin and other vitamin-K-antagonist effects via increased catabolism of clotting factors) [25].

Pregnancy. Combination T4+T3 regimens are not contraindicated outright in pregnancy but are typically transitioned to L-T4 monotherapy before conception or in early pregnancy because T3 does not cross the placenta as readily as T4 and is inadequate to support first-trimester fetal thyroid hormone needs [30]. Untreated maternal hypothyroidism harms fetal neurodevelopment and is itself a strong indication to maintain (with L-T4) adequate maternal thyroid hormone replacement [25].

Obesity is not an appropriate indication for thyroid hormone therapy of any kind. The Synthroid and Cytomel labels both warn that thyroid hormones are not appropriate for treatment of obesity, alone or combined with other drugs, and that such use may be hazardous [5154]. The historical 'rainbow diet pill' combination of thyroid hormone with sympathomimetic amines is contraindicated [25].

Drug interactions

Anticoagulants: thyroid hormone potentiates the anticoagulant effect of warfarin and other vitamin-K-antagonists by increasing the catabolism of vitamin K-dependent clotting factors. INR should be monitored closely when initiating, titrating, or discontinuing a combination T4/T3 regimen in anticoagulated patients.

Insulin and oral hypoglycemic agents: combination thyroid hormone replacement may increase insulin or oral hypoglycemic requirements as hypothyroidism resolves. Reassess glucose control during titration.

Bile acid sequestrants (cholestyramine, colestipol), calcium and iron supplements, proton pump inhibitors, sucralfate, aluminum-containing antacids, and oral estrogen: these and other agents affect absorption or transport of thyroid hormones and require dose-time separation or dose adjustment. The interaction profile is similar to that of L-T4 monotherapy and is detailed in the Synthroid and Cytomel labels [5154].

Sympathomimetic amines: combination of thyroid hormone with sympathomimetic amines for obesity is contraindicated due to cardiovascular risk [5154].

Antidepressants: in the off-label depression-augmentation context, T3 has been used with tricyclic antidepressants [40] and with SSRIs (Cooper-Kazaz 2007) [4042]; clinicians should monitor for serotonergic and adrenergic symptoms during initiation.

Adverse events

Adverse events with combination T4/T3 therapy are predominantly the predictable signs and symptoms of relative hyperthyroidism, dose-related, and occur most commonly during dose titration or with chronic over-replacement: palpitations, tachycardia, atrial fibrillation (especially in older adults), tremor, heat intolerance, sweating, weight loss, increased appetite, insomnia, anxiety, irritability, menstrual irregularity, diarrhea, and accelerated bone resorption [13]. The T3 component contributes the post-dose adrenergic effects most prominently when an immediate-release T3 fraction is used [17]; sustained-release compounded T3 attenuates this signal.

Cardiovascular: atrial fibrillation in older adults is the most clinically important arrhythmia signal associated with thyroid hormone excess [4546]. The Flynn 2010 JCEM analysis linked suppressed TSH on long-term thyroxine therapy to cardiovascular morbidity and fracture risk [16 78]. Angina precipitation is a concern in patients with established ischemic heart disease starting therapy; the recommended starting dose in such patients is the lowest effective total dose with slow titration [9].

Bone: chronic over-replacement is associated with reduced bone mineral density and increased fracture risk, particularly in postmenopausal women and older men [1647]. This is a pharmacologic effect of suppressed TSH and elevated FT3 on osteoclast activity.

Allergic / hypersensitivity reactions to levothyroxine or liothyronine themselves are rare; reactions to excipients (lactose, modified food starch, calcium sulfate, dyes) in the manufactured tablets are more common and are one of the documented indications for compounded allergen-free combination preparations [5154 5].

Trial-level safety. Across the combination-therapy trial sequence [2], adverse-event profiles were generally similar between combination and monotherapy arms, with no signal of differential serious adverse events at the doses studied. The Akirov 2019 IPD meta-analysis [35] confirmed this overall safety pattern.

Adverse events with compounded sustained-release T4/T3 combination capsules specifically are not characterized in published controlled-trial datasets. Theoretical concerns include unpredictable release profile if the formulation has not been adequately characterized, pharmacy-specific stability and release data are the principal mitigation. Content-uniformity testing is essential because levothyroxine is classified by FDA as a narrow-therapeutic-index drug [55 638].

Monitoring Compounded T3/T4 Combinations Therapy

Baseline assessment should document the etiology of hypothyroidism (autoimmune, post-ablative, post-surgical, central), age, cardiovascular status, current thyroid medications and prior trials, the rationale for combination therapy, and the explicit therapeutic goal [25]. Baseline labs include TSH, free T4, free T3, and where relevant lipid panel and HbA1c. In athyreotic patients, the baseline FT3 and FT3/FT4 ratio are particularly informative per the Gullo 2011 [18] and Ito 2019 [3334] data.

On therapy under a combination regimen, TSH alone is incomplete because the post-dose T3 peak from any immediate-release T3 component transiently suppresses TSH [25]. Many clinicians supplement with free T3 and free T4 measurements, with FT3 ideally drawn at trough (before the next dose) or at a consistent time-of-day relative to dosing. The 2021 ATA/ETA/BTA consensus document [37] and the Hoermann 2015 HPT-axis modeling work [27] both note the limitations of TSH-only monitoring under combination regimens.

Reassessment intervals: 6, 8 weeks after any dose change; 6, 12 months once stable [25]. For combination-therapy trials, a pre-specified 3, 6 month review with symptom and laboratory endpoints determines whether the trial is continued or the patient is returned to L-T4 monotherapy per the 2021 consensus framework.

Cardiovascular: in patients with ischemic heart disease or atrial fibrillation history, ECG and clinical reassessment of arrhythmia and angina symptoms at each titration step are appropriate [25]. Patients should be counseled to report new palpitations, dyspnea, or chest pain.

Bone: chronic suppressed TSH should be avoided unless TSH suppression is the explicit goal (e.g., post-thyroidectomy thyroid cancer protocol per the 2015 ATA differentiated-thyroid-cancer guideline [29]) [25]. DEXA every 1, 2 years is reasonable in postmenopausal women and older men with chronically suppressed TSH on combination or supraphysiologic therapy.

Compounded T3/T4 Combinations in Special Populations

Compounded T3/T4 Combinations Evidence Quality

Evidence supporting the individual FDA-approved single-hormone products (Synthroid, Tirosint, Cytomel and generics) is strong [5][15][25][4]. Evidence supporting desiccated thyroid extract as a 4.2:1 fixed-ratio combination is observational plus a small randomized comparison [23] showing patient preference signal without mean symptom-score advantage over L-T4. The combination T4+T3 trial sequence using separately dosed L-T4 and L-T3 is substantial: Bunevicius 1999 [2], Walsh 2003 [5], Clyde 2003 [6], Siegmund 2004 (14:1 molar ratio) [7], Saravanan 2005 (n=697, largest combination-therapy RCT) [8], Appelhof 2005 [9], Nygaard 2009 [13], and Shakir 2021 [38], predominantly null on objective primary endpoints. Meta-analyses by Grozinsky-Glasberg 2006 [11], Ma 2009 [15], and Akirov 2019 (individual-patient-data) [35] confirm no consistent population-level advantage of combination over monotherapy in unselected hypothyroid patients.

Patient preference frequently favors combination in crossover designs [2]. This preference signal is not aligned with the objective-endpoint trial results and is interpreted variously as a placebo or expectancy effect, a small genuine effect not captured by standardized instruments, or a genuine responder phenotype masked by averaging across unselected populations. Hennessey 2023 [39] and Peterson 2018 [32] document the persistent patient-side dissatisfaction signal on L-T4 monotherapy.

The DIO2 Thr92Ala polymorphism candidate-moderator signal [14] [14] is biologically plausible and the strongest available patient-selection signal but has not been prospectively replicated; Appelhof 2005 DIO2 subanalysis on a different dataset did not support it [10]. Population genotyping is not recommended [2537]. Athyreotic patients are the subgroup with the most defensible biochemical case for combination therapy per Gullo 2011 [18] and Ito 2019 [3334].

Evidence supporting compounded synthetic T4/T3 combination capsules specifically, as opposed to the broader combination-therapy concept, is limited. The combination-therapy trials used separately dosed L-T4 and L-T3 tablets. The compounded single-capsule formulation is an extrapolation supported by the underlying ratio rationale [1], the pharmacokinetic-flattening rationale for sustained-release T3 [17], and the practical adherence advantage of a single capsule, but is not directly tested in a published phase-3-equivalent trial. The 2021 ATA/ETA/BTA consensus document [37] acknowledges sustained-release liothyronine preparations as a clinically reasonable approach when the immediate-release manufactured product is suboptimal.

Major Compounded T3/T4 Combinations Clinical Studies

Study	Design	Participants	Duration	Finding
Pilo et al. (1990, Am J Physiol)	Multicompartmental kinetic analysis of T4 and T3 turnover in human volunteers	—	—	Established that the healthy human thyroid gland secretes T4 and T3 in approximately a 14:1 molar ratio, physiologic-ratio rationale for synthetic combination preparations at 12:1 to 14:1 [1]
Bunevicius et al. (1999, NEJM)	Randomized double-blind crossover substituting 12.5 mcg T3 for 50 mcg T4 in standard L-T4 regimens	33	5 weeks per arm	Improved mood and neuropsychological function on partial T4-to-T3 substitution, generated the modern combination-therapy debate [2]
Bunevicius & Prange (2002, Endocrine)	Randomized crossover, T4 vs T4+T3 in post-thyroidectomy Graves disease patients	10	Crossover	Small follow-up trial in athyreotic-after-Graves population; mixed mood and cognitive findings [3]
Saravanan et al. (2002, Clin Endocrinol)	Large community-based controlled questionnaire study of psychological	397 cases, 551 controls	Cross-sectional	Patients on adequate L-T4 doses reported significantly worse psychological well-being than community

Study	Design	Participants	Duration	Finding
	well-being in patients on adequate L-T4 doses			controls, frames the unmet-need signal that motivates combination-therapy trials [4]
Walsh et al. (2003, JCEM)	Randomized double-blind crossover, T4 vs T4+T3 substitution	110	10 weeks per arm	No improvement in well-being, quality of life, or cognitive function on combined T4/T3 versus T4 alone [5]
Clyde et al. (2003, JAMA)	Randomized double-blind, parallel-group, L-T4 vs L-T4 plus liothyronine in primary hypothyroidism	46	4 months	No advantage of combination over monotherapy on cognitive performance, mood, or quality of life endpoints [6]
Siegmund et al. (2004, Clin Endocrinol), 14:1 molar ratio trial	Randomized double-blind crossover, L-T4 vs L-T4 + L-T3 at a bioavailable molar ratio of 14:1	23	12 weeks per arm	Replacement therapy with L-T4 + L-T3 at a 14:1 molar ratio was no better than L-T4 monotherapy in well-being or cognitive function, direct test of the physiologic-ratio hypothesis underlying compounded synthetic combinations [7]
Appelhof et al. (2005, JCEM)	Randomized double-blind, three-arm trial: L-T4 monotherapy vs two L-T4:L-T3 ratios (5:1 and 10:1)	141	15 weeks	No primary-endpoint benefit on well-being or neurocognitive functioning; patient preference favored combination therapy with weight loss as a likely driver [9]
Appelhof et al. (2005, JCEM), DIO2 polymorphism subanalysis	Genotype-stratified analysis of the Appelhof 2005 trial dataset for DIO2 polymorphisms	—	—	DIO2 polymorphisms not associated with well-being, neurocognitive functioning, or preference for combination therapy in this dataset [10]
Saravanan et al. (2005, JCEM), largest community-based	Randomized double-blind community-based parallel-group trial of partial L-T4-to-L-T3	697	12 months	Partial substitution of L-T4 with L-T3 did not improve general health, well-being, or hypothyroid symptoms in a large community-based

Study	Design	Participants	Duration	Finding
combination-therapy RCT	substitution vs L-T4 alone			primary hypothyroidism cohort [8]
Grozinsky-Glasberg et al. (2006, JCEM)	Systematic review and meta-analysis of 11 randomized controlled trials of combination T4+T3 vs T4 monotherapy	1216	Pooled across trials	No consistent benefit of combination over monotherapy on pain, depression, anxiety, fatigue, quality of life, body weight, total cholesterol, TSH, or body composition. Patient preference signal favoring combination was variable across trials [11].
Villar et al. (2007, Cochrane)	Cochrane systematic review of thyroid hormone replacement for subclinical hypothyroidism	—	—	Replacement improved some lipid parameters and surrogate cardiac function markers but did not consistently improve survival, cardiovascular morbidity, or health-related quality of life, context for the broader hypothyroidism replacement-therapy evidence base [12]
Nygaard et al. (2009, Eur J Endocrinol)	Randomized double-blind crossover, T4 vs T4+T3	59	12 weeks per arm	Combination therapy was preferred by 49% of patients vs 15% preferring monotherapy; modest improvement in some quality-of-life domains [13]
Panicker et al. (2009, JCEM), DIO2 polymorphism reanalysis	Reanalysis of the Saravanan/Bunevicius combined-therapy datasets stratified by DIO2 Thr92Ala (rs225014) genotype	—	—	DIO2 Thr92Ala homozygotes had lower baseline psychological well-being on L-T4 monotherapy and reported greater symptomatic benefit from T4+T3 combination therapy than non-carriers, strongest available signal of a responder phenotype [14]
	Meta-analysis of randomized trials of T4	—	—	No statistically significant difference in symptom scores,

Study	Design	Participants	Duration	Finding
Ma et al. (2009, Nucl Med Commun)	monotherapy versus T4+T3 combination			lipid profile, body weight, or quality of life between regimens [15]
Celi et al. (2011, JCEM)	Randomized double-blind crossover, thrice-daily liothyronine vs once-daily levothyroxine at TSH-equivalent doses	14	Crossover; multiple weeks per arm	Comparable TSH suppression; improvement in lipid panel and small improvement in body weight on the liothyronine arm; demonstrated that pharmacokinetically smoothed T3 dosing is feasible [17]
Gullo et al. (2011, PLoS One)	Cross-sectional analysis of FT3, FT4, FT3/FT4 ratio in athyreotic patients on L-T4 monotherapy vs euthyroid controls	1811 athyreotic, 3875 controls	Cross-sectional	Athyreotic patients on L-T4 monotherapy have significantly lower FT3 and FT3/FT4 ratio at any given TSH than euthyroid controls, biochemical evidence that L-T4 monotherapy does not fully normalize peripheral T3 in patients without a thyroid gland [18]
Hoang et al. (2013, JCEM)	Randomized double-blind crossover comparing desiccated thyroid extract (DTE) with L-T4 in primary hypothyroidism	70	16 weeks per arm	No mean difference in symptom and neuropsychological scores; 48.6% of patients preferred DTE; DTE arm produced modest weight loss [23]
Akirov et al. (2019, Front Endocrinol), individual-patient-data meta-analysis	Individual-patient-data meta-analysis of randomized trials of combination L-T4 + L-T3 vs L-T4 monotherapy	—	—	No statistically significant advantage of combination therapy on mood, cognition, or general well-being at the IPD level; preference signal not aligned with objective endpoints [35]
Shakir et al. (2021, JCEM), three-arm crossover	Randomized double-blind three-arm crossover: L-T4,	75	Three 22-week arms	No clinically meaningful between-arm differences in symptom or quality-of-life measures; patient preferences

Study	Design	Participants	Duration	Finding
	desiccated thyroid extract, and L-T4 + L-T3			distributed across the three regimens [38]
Jonklaas et al. (2014, Thyroid), ATA hypothyroidism guidelines	Evidence-based clinical practice guidelines	—	—	L-T4 monotherapy recommended as first-line for primary hypothyroidism; routine use of combination L-T4+L-T3 not recommended, with a trial permitted in selected patients [25]
Garber et al. (2012, Thyroid), AACE/ATA hypothyroidism guidelines	Joint clinical practice guidelines	—	—	Endorses L-T4 monotherapy as first-line for hypothyroidism; combination therapy considered for individualized cases [21]
Wiersinga et al. (2012, Eur Thyroid J), ETA combination-therapy guidelines	Evidence-based clinical practice guidelines	—	—	Permits a trial of L-T4 + L-T3 combination therapy in patients with persistent symptoms despite L-T4 monotherapy and biochemical euthyroidism [22]
Pearce et al. (2013, Eur Thyroid J), ETA subclinical hypothyroidism guidelines	Evidence-based clinical practice guidelines	—	—	Framework for diagnosing and managing subclinical hypothyroidism, including replacement-therapy thresholds, context for the broader hypothyroidism replacement-therapy literature [24]
Jonklaas, Bianco, Cappola et al. (2021, Thyroid / Eur Thyroid J), joint ATA/ETA/ BTA consensus	Consensus document on evidence-based use of L-T4/L-T3 combinations	—	—	Conditional, individualized approach: trial of combination therapy reasonable in selected patients with persistent symptoms despite adequate L-T4 monotherapy, with pre-specified endpoints and trial duration; sustained-release liothyronine recognized as a reasonable formulation approach; population-level

Study	Design	Participants	Duration	Finding
				DIO2 genotyping not recommended [37]
Hennessey (2015, Endocr Pract)	Historical and current perspective	—	—	Reviews thyroid extract and modern compounded thyroid hormone preparations including sustained-release liothyronine as alternatives to standard L-T4 monotherapy [26]
Hennessey (2017, Endocrine)	Historical review	—	—	Documents the emergence of levothyroxine as the standard thyroid hormone replacement therapy, displacing desiccated thyroid extract [31]
Hennessey (2023, Endocr Pract)	Practitioner-facing review	—	—	Surveys L-T4 monotherapy effectiveness and the unmet-need literature for combination-therapy and DTE alternatives [39]
Peterson et al. (2018, Thyroid)	Online survey of hypothyroid patients	—	—	Documents prominent dissatisfaction on L-T4 monotherapy in a self-selected respondent cohort, patient-side signal complementing the trial-level evidence [32]
Hoermann et al. (2015, Front Endocrinol)	Modeling and clinical analysis of HPT axis homeostasis under L-T4 monotherapy	—	—	TSH-only targeting can leave a meaningful subset of patients with discordant FT3 status, supports individualized monitoring under combination regimens [27]
McAninch & Bianco (2015, Lancet Diabetes Endocrinol)	Review	—	—	Integrates clinical, biochemical, and DIO2-polymorphism strands into a unifying account of why L-T4 monotherapy is sufficient for most hypothyroid patients but leaves a subset with

Study	Design	Participants	Duration	Finding
				biochemically detectable peripheral T3 deficit and persistent symptoms [28]
Ettleson & Bianco (2020, JCEM)	Narrative review of individualized therapy for hypothyroidism	—	—	Survey of unmet need on L-T4 monotherapy and pragmatic recommendations for trial of combination therapy in selected patients, frames the clinical case for compounded combination preparations [36]
Ito et al. (2019, Thyroid)	Serum thyroid hormone balance in athyreotic patients on L-T4 monotherapy after radioiodine for Graves disease	—	—	Athyreotic patients had lower FT3 and FT3/FT4 ratio than euthyroid controls, confirms Gullo 2011 in a separate cohort [34]
Ito et al. (2019, Endocr J)	Symptom and FT3 analysis in athyreotic L-T4-treated patients	—	—	Subset of athyreotic patients reported residual hypothyroid symptoms despite TSH in the reference range, correlated with lower FT3 [33]
Escobar-Morreale et al. (1995, J Clin Invest)	Preclinical thyroidectomized-rat study comparing L-T4 monotherapy vs L-T4 + L-T3 on tissue T3 concentrations	—	—	L-T4 monotherapy did not normalize tissue T3 concentrations in all organs of thyroidectomized rats, mechanistic foundation for clinical interest in combination therapy [44]
Flynn et al. (2010, JCEM)	Population cohort analysis linking serum TSH on long-term L-T4 therapy to cardiovascular morbidity and fracture risk	Population cohort	Long-term follow-up	Suppressed TSH on long-term thyroxine therapy associated with increased cardiovascular disease, dysrhythmias, and fractures, informs the recommendation to avoid chronic TSH suppression unless required [16]
	Review of subclinical thyroid dysfunction	—	—	Catalogs cardiovascular and bone consequences of

Study	Design	Participants	Duration	Finding
Biondi & Cooper (2008, Endocr Rev)				chronically suppressed TSH, frames the safety boundary of T3-containing regimens [47]
Sawin (2002, Thyroid) / Surks et al. (2004, JAMA)	Review / cohort analyses of atrial fibrillation in subclinical hyperthyroidism and the AACE/ATA/Endocrine Society consensus on subclinical thyroid disease	—	—	Suppressed TSH is associated with atrial fibrillation in older adults, relevant to avoiding over-replacement on chronic T3-containing therapy [4546]
Joffe et al. (1993, Arch Gen Psychiatry)	Randomized double-blind placebo-controlled comparison of T3, lithium, and placebo augmentation of tricyclic antidepressants in refractory unipolar depression	50	2 weeks augmentation	T3 and lithium augmentation both superior to placebo for response in refractory depression, relevant to T3-augmentation use cases that may use a combination capsule [40]
Aronson et al. (1996, Arch Gen Psychiatry)	Meta-analysis of 8 controlled trials of T3 augmentation in depression	—	—	Small but statistically significant augmentation effect of T3 in refractory depression [41]
Cooper-Kazaz et al. (2007, Arch Gen Psychiatry)	Randomized double-blind placebo-controlled trial of combined sertraline + T3 from treatment initiation vs sertraline alone in major depression	124	8 weeks	Combined sertraline + T3 superior to sertraline alone on depression rating scales and response/remission rates [42]
Nierenberg et al. (2006, Am J Psychiatry), STAR*D level 3	Randomized open-label comparison of T3 augmentation vs lithium augmentation in major depression after two failed antidepressant trials	142	14 weeks	Remission rates approximately 25% for T3 and approximately 16% for lithium (non-significant difference); T3 was better tolerated [43]
		—	—	

Study	Design	Participants	Duration	Finding
Alexander et al. (2017, Thyroid), ATA pregnancy guidelines	Evidence-based clinical practice guidelines			Framework for diagnosing and managing thyroid disease during pregnancy and postpartum, informs the recommendation to transition combination regimens to L-T4 monotherapy before conception or in early pregnancy [30]
Haugen et al. (2015, Thyroid), ATA differentiated thyroid cancer guidelines	Evidence-based clinical practice guidelines	—	—	Provides TSH-suppression targets in post-thyroidectomy differentiated thyroid cancer, defines the explicit clinical context in which TSH suppression is a legitimate therapeutic goal [29]

Compounded T3/T4 Combinations Pharmacokinetics & Pharmacodynamics

Pharmacokinetics

Each active component has its own pharmacokinetic profile. Levothyroxine has a terminal half-life of approximately 7 days, supports stable once-daily dosing, and is approximately 70, 80% absorbed from the upper small intestine on a fasting stomach; absorption is reduced by concurrent food, calcium, iron, proton pump inhibitors, and bile acid sequestrants [51]. Liothyronine is rapidly absorbed (Tmax 2, 4 hours) with approximately 95% bioavailability on a fasting stomach and a terminal half-life of approximately 24 hours in euthyroid adults [5417].

The principal PK consideration specific to combination preparations is the post-dose serum T3 peak from the T3 component. Immediate-release liothyronine produces a 30, 40% above-baseline peak in serum T3 within 2, 4 hours of dosing [17]; a compounded combination capsule with an immediate-release T3 fraction inherits this profile. Compounded sustained-release T3, formulated with hydrophilic-matrix or coated-bead excipients, is designed to extend T3 absorption across 8, 24 hours and attenuate the peak. The release profile depends on the specific compounded formulation and is documented per the pharmacy's product-specific data.

Compounded combination capsules are not bioequivalent to any FDA-approved single-hormone product or to desiccated thyroid extract. PK characteristics published for Synthroid, Cytomel, or desiccated thyroid extract should not be assumed to translate without local stability and content-uniformity data.

Levothyroxine is classified by FDA as a narrow-therapeutic-index drug [55], which elevates the importance of consistent compounded formulation between batches.

Pharmacodynamics

Pharmacodynamic effects are those of thyroid hormone in general: nuclear thyroid hormone receptor (TRα, TRβ) occupancy and downstream regulation of TRE-containing target genes, producing increased basal metabolic rate, increased cardiac output (positive chronotropy and inotropy), enhanced lipolysis and hepatic LDL clearance, modulation of central catecholamine sensitivity, and acceleration of bone turnover [17]. The T3 component contributes the most direct receptor occupancy; the T4 component supplies sustained substrate for peripheral deiodination to T3 [49].

Measured pharmacodynamic endpoints in clinical practice are TSH, free T4, and free T3 (trough draw preferred for FT3 under combination regimens). Patient-reported symptoms, energy, mood, cognitive function, cold intolerance, weight, are weighted alongside the laboratory metrics in individualized titration. TSH-only monitoring is incomplete under combination therapy because the post-dose T3 peak transiently suppresses TSH [37][27][17].

↓↑ Comparing Compounded T3/T4 Combinations Formulations

The combination-therapy treatment options can be ranked by formulation type. (1) Two separate FDA-approved tablets, Synthroid (or generic levothyroxine, Tirosint, Tirosint-SOL) plus Cytomel (or generic liothyronine), taken at the same or offset times [5][15][35][4]. Advantages: FDA-approved single-hormone products with extensive labeling and bioequivalence data. Disadvantages: two prescriptions, two adherence points, the post-dose serum T3 peak from immediate-release Cytomel [17]. (2) Desiccated thyroid extract (Armour Thyroid, NP Thyroid, Nature-Throid), an FDA-approved porcine fixed-ratio combination at approximately 4.2:1 T4:T3 by weight [26]. Advantages: FDA-approved combination product. Disadvantages: porcine-derived; non-physiologic ratio (substantially more T3 per unit T4 than the human 14:1 molar ratio per Pilo 1990 [1]); variable T3 content has been reported historically; the Hoang 2013 [23] and Shakir 2021 [38] trials show no objective endpoint advantage over L-T4 monotherapy but a patient-preference signal. (3) Compounded synthetic T4/T3 combination capsule at a custom physiologic ratio (typically 12:1 to 14:1 by weight) with optional sustained-release T3 component. Advantages: physiologic ratio, synthetic-only ingredients, allergen-free options, single-capsule simplification, optional PK-flattening sustained-release T3. Disadvantages: not FDA-approved; no fixed-ratio published efficacy data specific to compounded synthetic combinations; requires documented patient-specific clinical rationale under 503A [57].

Compounded sustained-release combination capsules are the most pharmacokinetically differentiated option [52]. They attenuate the post-dose T3 peak [17] and are recognized by the 2021 ATA/ETA/BTA consensus document as a clinically reasonable approach [37] where the immediate-release manufactured product is suboptimal.

Compounded T3/T4 Combinations Storage and Handling

Manufactured Synthroid, Cytomel, generic levothyroxine, generic liothyronine, and desiccated thyroid extract are stored at 20, 25°C (68, 77°F) with excursions permitted to 15, 30°C, protected from light and moisture, per labeling [51][54]. Compounded T4/T3 combination capsules are stored per the pharmacy's product-specific stability data and beyond-use date assignment under USP <795>; controlled room temperature storage is typical for capsule preparations [58].

Thyroid hormone capsules are not cold-chain products in the same sense as biologics or sterile injectables; standard controlled room temperature storage is sufficient for the manufactured tablets and most compounded combination capsules [58].

Compounded T3/T4 Combinations Compounding & Operations

503A compounding

Compounded synthetic T4/T3 combination capsules are prepared under 503A on patient-specific prescriptions in state-licensed compounding pharmacies. RonanRx prepares oral capsules per USP General Chapter <795> (Pharmaceutical Compounding, Nonsterile Preparations), with documented active ingredient sourcing of levothyroxine sodium USP and liothyronine sodium USP from FDA-registered facilities, gravimetric verification of fill, content uniformity testing per the pharmacy's quality-management system, and full lot traceability from API source through dispensing [58].

Sustained-release T3 component formulations require additional product-specific documentation: the release-modifying excipient and ratio, beyond-use date supported by stability data, and the release profile (in vitro dissolution or otherwise documented). The 2021 ATA/ETA/BTA consensus document [37] acknowledges the absence of a manufactured sustained-release T3 or sustained-release combination product in the United States and recognizes compounded sustained-release preparations as a clinically reasonable approach for combination therapy [58].

Levothyroxine is classified by FDA as a narrow-therapeutic-index drug [55]; consistency of compounded combination batches is therefore a particular focus of the pharmacy's quality system, including content-uniformity testing and documentation of the T4:T3 weight ratio achieved in each batch [56]. Beyond-use dating, ingredient identity verification, and stability assessment follow USP <795>. Each compounded batch is documented per state board of pharmacy retention rules.

Pharmacist review

Each prescription for a compounded T4/T3 combination capsule undergoes pharmacist review prior to dispensing. The review confirms: a documented patient-specific clinical reason that separately dosed

Synthroid plus Cytomel, or desiccated thyroid extract, is not appropriate (custom physiologic ratio, sustained-release T3 component, allergen-free formulation, or single-capsule simplification with documented adherence rationale); absence of contraindications (uncorrected adrenal insufficiency, untreated thyrotoxicosis, acute MI; pregnancy is a relative indication to transition to L-T4 monotherapy [30]); appropriate concomitant medication review (anticoagulants, insulin and oral hypoglycemics, oral contraception or estrogen therapy, sympathomimetic agents, calcium/iron/PPIs affecting absorption); and a prescribed regimen consistent with the 2021 ATA/ETA/BTA consensus framework [37] for combination therapy.

RonanRx does not fill prescriptions that read as routine substitution of a compounded combination for the FDA-approved single-hormone products without documented clinical rationale, consistent with FDA guidance on compounded copies of commercially available drugs [57]. Custom physiologic-ratio capsules, sustained-release T3 component capsules, and allergen-free combinations are the well-defined 503A roles for compounded T4/T3 combinations that meet the patient-specific clinical need threshold. The narrow-therapeutic-index status of levothyroxine [55] is a pharmacist-review check on content uniformity for each batch.

Quality and traceability

Active pharmaceutical ingredients, levothyroxine sodium USP and liothyronine sodium USP, are sourced from FDA-registered facilities with documented certificates of analysis. Each compounded combination batch is recorded with lot numbers traceable to API source (separately for L-T4 and L-T3), compounding date, beyond-use date, content uniformity test result, T4:T3 ratio achieved, and dispensing pharmacist of record. Finished product lot records are retained per state board of pharmacy retention requirements. Sustained-release combination batches additionally include the release-modifying excipient lot, the fill weight per capsule, and the assigned beyond-use date supported by product-specific stability data.

Cold chain

Compounded T4/T3 combination capsules are stable at controlled room temperature and do not require cold-chain transport. The dispensing label and patient counseling specify standard controlled-room-temperature storage with protection from light and moisture, matching the storage profile of the manufactured single-hormone tablets [5154] [58].

Frequently Asked Questions About Compounded T3/T4 Combinations

Why would my doctor prescribe a compounded T4/T3 combination instead of just Synthroid?

Most people with hypothyroidism feel well on Synthroid (levothyroxine) alone [22]. A subset still feel unwell on T4 alone despite a normal TSH lab. For those patients, clinicians may consider adding T3, either as a separate Cytomel tablet, as desiccated thyroid extract (Armour, NP Thyroid), or as a compounded synthetic

capsule that contains both T4 and T3 at a custom ratio [25]. The 2012 ETA guideline, the 2014 ATA guideline, and the 2021 joint ATA/ETA/BTA consensus document all permit a trial of combination therapy in selected patients [37].

How is a compounded T4/T3 combination different from Armour Thyroid or NP Thyroid?

Armour Thyroid and NP Thyroid are FDA-approved porcine desiccated thyroid extract products at a fixed 4.2:1 T4:T3 weight ratio that reflects the porcine thyroid gland [2623]. Compounded synthetic T4/T3 capsules contain pharmaceutical-grade synthetic levothyroxine and liothyronine at a custom ratio, commonly 12:1 to 14:1 by weight, closer to the human glandular ratio of approximately 14:1 per Pilo's 1990 kinetic analysis [1]. They are synthetic-only (no porcine material), can be made allergen-free, and can include a sustained-release T3 component.

Why a 12:1 to 14:1 ratio? Where does that come from?

Pilo and colleagues' 1990 multicompartmental kinetic analysis of human thyroid hormone production established that the healthy human thyroid gland secretes T4 and T3 in approximately a 14:1 molar ratio [1]. Compounded synthetic combinations at 12:1 to 14:1 by weight approximate that physiologic ratio. Porcine desiccated thyroid extract at 4.2:1 is substantially T3-richer than the human gland [26].

Does adding T3 actually help symptoms?

It depends. The 1999 Bunevicius NEJM trial reported mood and cognitive benefit, but multiple larger trials (Walsh 2003, Clyde 2003, Siegmund 2004 testing a 14:1 ratio, Saravanan 2005 with n=697, Appelhof 2005, Nygaard 2009, Shakir 2021) and meta-analyses (Grozinsky-Glasberg 2006, Ma 2009, Akirov 2019 individual-patient-data) did not show consistent improvement in unselected populations [278]. Patient preference frequently favors combination in crossover trials [1135]. The 2021 joint consensus document supports a trial in selected patients with pre-specified endpoints [37].

Why a sustained-release T3 component?

Immediate-release liothyronine (Cytomel) produces a peak in serum T3 about 2, 4 hours after dosing that is roughly 30, 40% above baseline, a level a healthy gland does not produce. Sustained-release compounded T3 spreads absorption across the day to produce steadier levels. The 2021 ATA/ETA/BTA consensus document acknowledges the PK limitations of immediate-release liothyronine and recognizes sustained-release preparations as a clinically reasonable approach [1737].

What about the DIO2 polymorphism, should I be tested?

Panicker 2009 reported that DIO2 Thr92Ala homozygotes had lower baseline well-being on L-T4 monotherapy and greater symptomatic benefit from combination therapy than non-carriers [1410]. The Appelhof 2005 DIO2 subanalysis on a different dataset did not replicate the finding. No prospectively

powered genotype-stratified trial has confirmed the responder phenotype. The 2014 ATA, 2012 ETA, and 2021 joint consensus do not recommend population genotyping [37].

When is a compounded T4/T3 combination appropriate under 503A?

Per FDA guidance, a compounded preparation is appropriate when the prescriber documents a patient-specific clinical need that the FDA-approved single-hormone products or desiccated thyroid extract cannot meet [57]. For T4/T3 combinations, the documented needs are typically a custom physiologic ratio (12:1 to 14:1 by weight), a sustained-release T3 component, an allergen-free formulation, or a single-capsule simplification with documented adherence rationale. Cost or preference alone does not qualify [56].

Is a compounded T4/T3 combination safe in pregnancy?

Combination T4+T3 regimens are typically transitioned to L-T4 monotherapy before conception or in early pregnancy because T3 does not cross the placenta as readily as T4 and is inadequate to support first-trimester fetal thyroid hormone needs [3025]. Untreated maternal hypothyroidism harms fetal neurodevelopment, so the underlying hypothyroidism is treated through pregnancy, typically with L-T4 alone, dose-adjusted by trimester, per the 2017 ATA pregnancy guideline.

How is monitoring different on a combination regimen?

TSH alone is incomplete under combination therapy because the post-dose T3 peak transiently suppresses TSH. Clinicians supplement with free T3 (ideally drawn at trough, before the next dose) and free T4. Reassessment intervals are 6, 8 weeks after any dose change and 6, 12 months once stable, with a pre-specified 3, 6 month combination-therapy trial review per the 2021 consensus framework [3727].

Does RonanRx sell compounded T4/T3 combination capsules directly to patients?

No. Compounded T4/T3 combination capsules require a patient-specific prescription from a licensed doctor for an identified patient with a documented clinical reason the FDA-approved single-hormone products or desiccated thyroid extract are not appropriate, plus pharmacist review before dispensing [57]. RonanRx is not a direct-to-consumer storefront [56].

References

1. *[pilo1990]* Pilo A, Iervasi G, Vitek F, Ferdeghini M, Cazzuola F, Bianchi R. *Thyroidal and peripheral production of 3,5,3'-triiodothyronine in humans by multicompartmental analysis*. American Journal of Physiology. 1990. PMID 2333963. (accessed 2026-05-11)
2. *[bunevicius1999]* Bunevicius R, Kazanavicius G, Zalinkevicius R, Prange AJ Jr. *Effects of thyroxine as compared with thyroxine plus triiodothyronine in patients with hypothyroidism*. New England Journal of Medicine. 1999. PMID 9971866. (accessed 2026-05-11)

3. *[bunevicius2002]* Bunevicius R, Jakubonien N, Jurkevicius R, Cernicat J, Lasas L, Prange AJ Jr. *Thyroxine vs thyroxine plus triiodothyronine in treatment of hypothyroidism after thyroidectomy for Graves' disease*. Endocrine. 2002. PMID 12374459. (accessed 2026-05-11)
4. *[saravanan2002]* Saravanan P, Chau WF, Roberts N, Vedhara K, Greenwood R, Dayan CM. *Psychological well-being in patients on 'adequate' doses of l-thyroxine: results of a large, controlled community-based questionnaire study*. Clinical Endocrinology (Oxford). 2002. PMID 12390330. (accessed 2026-05-11)
5. *[walsh2003]* Walsh JP, Shiels L, Lim EM, Bhagat CI, Ward LC, Stuckey BG, Dhaliwal SS, Chew GT, Bhagat MC, Cussons AJ. *Combined thyroxine/liothyronine treatment does not improve well-being, quality of life, or cognitive function compared to thyroxine alone: a randomized controlled trial in patients with primary hypothyroidism*. Journal of Clinical Endocrinology and Metabolism. 2003. PMID 14557419. (accessed 2026-05-11)
6. *[clyde2003]* Clyde PW, Harari AE, Getka EJ, Shakir KM. *Combined levothyroxine plus liothyronine compared with levothyroxine alone in primary hypothyroidism: a randomized controlled trial*. JAMA. 2003. PMID 14665656. (accessed 2026-05-11)
7. *[siegmund2004]* Siegmund W, Spieker K, Weike AI, Giessmann T, Modess C, Dabers T, Kirsch G, Sänger E, Engel G, Hamm AO, Nauck M, Meng W. *Replacement therapy with levothyroxine plus triiodothyronine (bioavailable molar ratio 14 : 1) is not superior to thyroxine alone to improve well-being and cognitive performance in hypothyroidism*. Clinical Endocrinology (Oxford). 2004. PMID 15163340. (accessed 2026-05-11)
8. *[saravanan2005]* Saravanan P, Simmons DJ, Greenwood R, Peters TJ, Dayan CM. *Partial substitution of thyroxine (T4) with tri-iodothyronine in patients on T4 replacement therapy: results of a large community-based randomized controlled trial*. Journal of Clinical Endocrinology and Metabolism. 2005. PMID 15585551. (accessed 2026-05-11)
9. *[appelhof2005]* Appelhof BC, Fliers E, Wekking EM, Schene AH, Huyser J, Tijssen JG, Endert E, van Weert HC, Wiersinga WM. *Combined therapy with levothyroxine and liothyronine in two ratios, compared with levothyroxine monotherapy in primary hypothyroidism: a double-blind, randomized, controlled clinical trial*. Journal of Clinical Endocrinology and Metabolism. 2005. PMID 15705921. (accessed 2026-05-11)
10. *[appelhof2005_dio2]* Appelhof BC, Peeters RP, Wiersinga WM, Visser TJ, Wekking EM, Huyser J, Schene AH, Tijssen JG, Hoogendijk WJ, Fliers E. *Polymorphisms in type 2 deiodinase are not associated with well-being, neurocognitive functioning, and preference for combined thyroxine/3,5,3'-triiodothyronine therapy*. Journal of Clinical Endocrinology and Metabolism. 2005. PMID 16144953. (accessed 2026-05-11)
11. *[grozinsky2006]* Grozinsky-Glasberg S, Fraser A, Nahshoni E, Weizman A, Leibovici L. *Thyroxine-triiodothyronine combination therapy versus thyroxine monotherapy for clinical hypothyroidism: meta-analysis of randomized controlled trials*. Journal of Clinical Endocrinology and Metabolism. 2006. PMID 16670166. (accessed 2026-05-11)
12. *[villar2007cochrane]* Villar HC, Saconato H, Valente O, Atallah AN. *Thyroid hormone replacement for subclinical hypothyroidism*. Cochrane Database of Systematic Reviews. 2007. PMID 17636722. (accessed 2026-05-11)
13. *[nygaard2009]* Nygaard B, Jensen EW, Kvetny J, Jarløv A, Faber J. *Effect of combination therapy with thyroxine (T4) and 3,5,3'-triiodothyronine versus T4 monotherapy in patients with hypothyroidism, a double-blind, randomised cross-over study*. European Journal of Endocrinology. 2009. PMID 19666698. (accessed 2026-05-11)
14. *[panicker2009_dio2]* Panicker V, Saravanan P, Vaidya B, Evans J, Hattersley AT, Frayling TM, Dayan CM. *Common variation in the DIO2 gene predicts baseline psychological well-being and response to combination thyroxine plus triiodothyronine therapy in hypothyroid patients*. Journal of Clinical Endocrinology and Metabolism. 2009. PMID 19190113. (accessed 2026-05-11)
15. *[ma_combination_meta]* Ma C, Xie J, Huang X, Wang G, Wang Y, Wang X, Zuo S. *Thyroxine alone or thyroxine plus triiodothyronine replacement therapy for hypothyroidism*. Nuclear Medicine Communications. 2009. PMID 19491714. (accessed 2026-05-11)

16. *[flynn2010]* Flynn RW, Bonellie SR, Jung RT, MacDonald TM, Morris AD, Leese GP. *Serum thyroid-stimulating hormone concentration and morbidity from cardiovascular disease and fractures in patients on long-term thyroxine therapy*. Journal of Clinical Endocrinology and Metabolism. 2010. PMID 19906785. (accessed 2026-05-11)
17. *[celi2011]* Celi FS, Zemskova M, Linderman JD, Smith S, Drinkard B, Sachdev V, Skarulis MC, Kozlosky M, Csako G, Costello R, Pucino F. *Metabolic effects of liothyronine therapy in hypothyroidism: a randomized, double-blind, crossover trial of liothyronine versus levothyroxine*. Journal of Clinical Endocrinology and Metabolism. 2011. PMID 21865366. (accessed 2026-05-11)
18. *[gullo2011]* Gullo D, Latina A, Frasca F, Le Moli R, Pellegriti G, Vigneri R. *Levothyroxine monotherapy cannot guarantee euthyroidism in all athyreotic patients*. PLoS One. 2011. PMID 21829633. (accessed 2026-05-11)
19. *[gullo2017]* Gullo D, Latina A, Frasca F, Squatrito S, Belfiore A, Vigneri R. *Seasonal variations in TSH serum levels in athyreotic patients under L-thyroxine replacement monotherapy*. Clinical Endocrinology (Oxford). 2017. PMID 28398655. (accessed 2026-05-11)
20. *[biondi2012]* Biondi B, Wartofsky L. *Combination treatment with T4 and T3: toward personalized replacement therapy in hypothyroidism?*. Journal of Clinical Endocrinology and Metabolism. 2012. PMID 22593590. (accessed 2026-05-11)
21. *[garber2012aace]* Garber JR, Cobin RH, Gharib H, Hennessey JV, Klein I, Mechanick JI, Pessah-Pollack R, Singer PA, Woeber KA. *Clinical practice guidelines for hypothyroidism in adults: cosponsored by the American Association of Clinical Endocrinologists and the American Thyroid Association*. Thyroid. 2012. PMID 22954017. (accessed 2026-05-11)
22. *[wiersinga2012_eta]* Wiersinga WM, Duntas L, Fadeyev V, Nygaard B, Vanderpump MP. *2012 ETA Guidelines: The Use of L-T4 + L-T3 in the Treatment of Hypothyroidism*. European Thyroid Journal. 2012. PMID 24782999. (accessed 2026-05-11)
23. *[hoang2013]* Hoang TD, Olsen CH, Mai VQ, Clyde PW, Shakir MK. *Desiccated thyroid extract compared with levothyroxine in the treatment of hypothyroidism: a randomized, double-blind, crossover study*. Journal of Clinical Endocrinology and Metabolism. 2013. PMID 23539727. (accessed 2026-05-11)
24. *[pearce2013eta]* Pearce SH, Brabant G, Duntas LH, Monzani F, Peeters RP, Razvi S, Wemeau JL. *2013 ETA Guideline: Management of Subclinical Hypothyroidism*. European Thyroid Journal. 2013. PMID 24783053. (accessed 2026-05-11)
25. *[jonklaas2014_ata]* Jonklaas J, Bianco AC, Bauer AJ, Burman KD, Cappola AR, Celi FS, Cooper DS, Kim BW, Peeters RP, Rosenthal MS, Sawka AM. *Guidelines for the treatment of hypothyroidism: prepared by the American Thyroid Association task force on thyroid hormone replacement*. Thyroid. 2014. PMID 25266247. (accessed 2026-05-11)
26. *[hennessey2015]* Hennessey JV. *Historical and current perspective in the use of thyroid extracts for the treatment of hypothyroidism*. Endocrine Practice. 2015. PMID 26121440. (accessed 2026-05-11)
27. *[hoermann2015]* Hoermann R, Midgley JE, Larisch R, Dietrich JW. *Homeostatic control of the thyroid-pituitary axis: perspectives for diagnosis and treatment*. Frontiers in Endocrinology (Lausanne). 2015. PMID 26635726. (accessed 2026-05-11)
28. *[mcaninch2015]* McAninch EA, Bianco AC. *New insights into the variable effectiveness of levothyroxine monotherapy for hypothyroidism*. Lancet Diabetes and Endocrinology. 2015. PMID 26362364. (accessed 2026-05-11)
29. *[haugen2015ata]* Haugen BR, Alexander EK, Bible KC, Doherty GM, Mandel SJ, Nikiforov YE, Pacini F, Randolph GW, Sawka AM, Schlumberger M, Schuff KG, Sherman SI, Sosa JA, Steward DL, Tuttle RM, Wartofsky L. *2015 American Thyroid Association Management Guidelines for Adult Patients with Thyroid Nodules and Differentiated Thyroid Cancer: The American Thyroid Association Guidelines Task Force on Thyroid Nodules and Differentiated Thyroid Cancer*. Thyroid. 2015. PMID 26462967. (accessed 2026-05-11)

30. *[alexander2017ata]* Alexander EK, Pearce EN, Brent GA, Brown RS, Chen H, Dosiou C, Grobman WA, Laurberg P, Lazarus JH, Mandel SJ, Peeters RP, Sullivan S. *2017 Guidelines of the American Thyroid Association for the Diagnosis and Management of Thyroid Disease During Pregnancy and the Postpartum*. Thyroid. 2017. PMID 28056690. (accessed 2026-05-11)
31. *[hennessey2017_emergence]* Hennessey JV. *The emergence of levothyroxine as a treatment for hypothyroidism*. Endocrine. 2017. PMID 27981511. (accessed 2026-05-11)
32. *[peterson2018]* Peterson SJ, Cappola AR, Castro MR, Dayan CM, Farwell AP, Hennessey JV, Kopp PA, Ross DS, Samuels MH, Sawka AM, Taylor PN, Jonklaas J, Bianco AC. *An Online Survey of Hypothyroid Patients Demonstrates Prominent Dissatisfaction*. Thyroid. 2018. PMID 29620972. (accessed 2026-05-11)
33. *[ito2019]* Ito M, Kawasaki M, Danno H, Kohsaka K, Nakamura S, Kojima N, Sakamoto K, Hisakado M, Yoshioka W, Kudo T, Nishihara E, Fukata S, Nishikawa M, Nakamura H, Miyauchi A. *Thyroid function related symptoms during levothyroxine monotherapy in athyreotic patients*. Endocrine Journal. 2019. PMID 31270299. (accessed 2026-05-11)
34. *[ito_atrophic]* Ito M, Miyauchi A, Hisakado M, Yoshioka W, Kudo T, Nishihara E, Kihara M, Ito Y, Miya A, Fukata S, Nishikawa M, Nakamura H, Amino N. *Serum Thyroid Hormone Balance in Levothyroxine Monotherapy-Treated Patients with Atrophic Thyroid After Radioiodine Treatment for Graves' Disease*. Thyroid. 2019. PMID 31411123. (accessed 2026-05-11)
35. *[akirov2019]* Akirov A, Fazelzad R, Ezzat S, Thabane L, Sawka AM. *A Systematic Review and Meta-Analysis of Patient Preferences for Combination Thyroid Hormone Treatment for Hypothyroidism*. Frontiers in Endocrinology (Lausanne). 2019. PMID 31396154. (accessed 2026-05-11)
36. *[ettleson_bianco]* Ettleson MD, Bianco AC. *Individualized Therapy for Hypothyroidism: Is T4 Enough for Everyone?*. Journal of Clinical Endocrinology and Metabolism. 2020. PMID 32614450. (accessed 2026-05-11)
37. *[jonklaas2021_consensus]* Jonklaas J, Bianco AC, Cappola AR, Celi FS, Fliers E, Heuer H, McAninch EA, Moeller LC, Nygaard B, Sawka AM, Watt T, Dayan CM. *Evidence-Based Use of Levothyroxine/Liothyronine Combinations in Treating Hypothyroidism: A Consensus Document*. Thyroid. 2021. PMID 33276704. (accessed 2026-05-11)
38. *[shakir2021]* Shakir MKM, Brooks DI, McAninch EA, Fonseca TL, Mai VQ, Bianco AC, Hoang TD. *Comparative Effectiveness of Levothyroxine, Desiccated Thyroid Extract, and Levothyroxine+Liothyronine in Hypothyroidism*. Journal of Clinical Endocrinology and Metabolism. 2021. PMID 34185829. (accessed 2026-05-11)
39. *[hennessey2023]* Hennessey JV. *Levothyroxine Monotherapy: What Works Better for the Individual With Hypothyroidism?*. Endocrine Practice. 2023. PMID 37419564. (accessed 2026-05-11)
40. *[joffe1993]* Joffe RT, Singer W, Levitt AJ, MacDonald C. *A placebo-controlled comparison of lithium and triiodothyronine augmentation of tricyclic antidepressants in unipolar refractory depression*. Archives of General Psychiatry. 1993. PMID 8489327. (accessed 2026-05-11)
41. *[aronson1996]* Aronson R, Offman HJ, Joffe RT, Naylor CD. *Triiodothyronine augmentation in the treatment of refractory depression. A meta-analysis*. Archives of General Psychiatry. 1996. PMID 8792761. (accessed 2026-05-11)
42. *[cooper_kazaz2007]* Cooper-Kazaz R, Apter JT, Cohen R, Karagichev L, Muhammed-Moussa S, Grupper D, Drori T, Newman ME, Sackeim HA, Glaser B, Lerer B. *Combined treatment with sertraline and liothyronine in major depression: a randomized, double-blind, placebo-controlled trial*. Archives of General Psychiatry. 2007. PMID 17548749. (accessed 2026-05-11)
43. *[nierenberg2006_stard]* Nierenberg AA, Fava M, Trivedi MH, Wisniewski SR, Thase ME, McGrath PJ, Alpert JE, Warden D, Luther JF, Niederehe G, Lebowitz B, Shores-Wilson K, Rush AJ. *A comparison of lithium and T(3) augmentation following two failed medication treatments for depression: a STAR*D report*. American Journal of Psychiatry. 2006. PMID 16946176. (accessed 2026-05-11)

44. *[escobar_morreale_rat]* Escobar-Morreale HF, Obregón MJ, Escobar del Rey F, Morreale de Escobar G. *Replacement therapy for hypothyroidism with thyroxine alone does not ensure euthyroidism in all tissues, as studied in thyroidectomized rats*. Journal of Clinical Investigation. 1995. PMID 8675653. (accessed 2026-05-11)

45. *[sawin_afib]* Sawin CT. *Subclinical hyperthyroidism and atrial fibrillation*. Thyroid. 2002. PMID 12165113. (accessed 2026-05-11)

46. *[surks2004]* Surks MI, Ortiz E, Daniels GH, Sawin CT, Col NF, Cobin RH, Franklyn JA, Hershman JM, Burman KD, Denke MA, Gorman C, Cooper RS, Weissman NJ. *Subclinical thyroid disease: scientific review and guidelines for diagnosis and management*. JAMA. 2004. PMID 14722150. (accessed 2026-05-11)

47. *[biondi_cooper2008]* Biondi B, Cooper DS. *The clinical significance of subclinical thyroid dysfunction*. Endocrine Reviews. 2008. PMID 17991805. (accessed 2026-05-11)

48. *[biondi_klein2004]* Biondi B, Klein I. *Hypothyroidism as a risk factor for cardiovascular disease*. Endocrine. 2004. PMID 15249698. (accessed 2026-05-11)

49. *[bianco_dio2_review]* Bianco AC, Dumitrescu A, Gereben B, Ribeiro MO, Fonseca TL, Fernandes GW, Bocco BMLC. *Paradigms of Dynamic Control of Thyroid Hormone Signaling*. Endocrine Reviews. 2019. PMID 31033998. (accessed 2026-05-11)

50. *[dayan_panicker]* Dayan C, Panicker V. *Management of hypothyroidism with combination thyroxine (T4) and triiodothyronine (T3) hormone replacement in clinical practice: a review of suggested guidance*. Thyroid Research. 2018. PMID 29375671. (accessed 2026-05-11)

51. *[fda_label_synthroid]* U.S. Food and Drug Administration. *Synthroid (levothyroxine sodium) tablets — FDA Prescribing Information*. FDA Drug Approval Package. 2017. https://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=1e11ad30-1041-4520-10b0-8f9d30d30fcc (accessed 2026-05-11)

52. *[fda_label_tirosint]* U.S. Food and Drug Administration. *Tirosint (levothyroxine sodium) capsules — FDA Prescribing Information*. FDA Drug Approval Package. 2019. https://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=7a7ade79-0165-4e31-b84e-667416c00c7e (accessed 2026-05-11)

53. *[fda_label_tirosint_sol]* U.S. Food and Drug Administration. *Tirosint-SOL (levothyroxine sodium) oral solution — FDA Prescribing Information*. FDA Drug Approval Package. 2020. https://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=5d378add-f13d-40f2-99dc-0f2340ab44b7 (accessed 2026-05-11)

54. *[fda_label_cytomel]* Pfizer (King Pharmaceuticals). *Cytomel (liothyronine sodium tablets) — Prescribing Information*. DailyMed (U.S. National Library of Medicine). 2024. https://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=2bf6cf8c-5af6-4ff7-a917-1f25b6dd0ddc (accessed 2026-05-11)

55. *[fda_nti_levothyroxine]* U.S. Food and Drug Administration. *Levothyroxine Sodium Product Information — FDA Drug Safety and Availability*. FDA Drug Safety. 2017. https://www.fda.gov/drugs/postmarket-drug-safety-information-patients-and-providers/levothyroxine-sodium-product-information (accessed 2026-05-11)

56. *[fda503a]* U.S. Food and Drug Administration. *Compounding Laws and Policies — Section 503A of the Federal Food, Drug, and Cosmetic Act*. FDA Drug Compounding. 2024. https://www.fda.gov/drugs/human-drug-compounding/compounding-laws-and-policies (accessed 2026-05-11)

57. *[fda_essentially_a_copy]* U.S. Food and Drug Administration. *Compounded Drug Products That Are Essentially Copies of Approved Drug Products Under Section 503A of the Federal Food, Drug, and Cosmetic Act — Guidance for Industry*. FDA Guidance for Industry. 2018. https://www.fda.gov/media/98973/download (accessed 2026-05-11)

58. *[usp_795]* United States Pharmacopeia. *USP General Chapter <795> Pharmaceutical Compounding — Nonsterile Preparations*. USP Compounding Compendium. 2023. https://www.usp.org/compounding/general-chapter-795 (accessed 2026-05-11)

How to Access Compounded T3/T4 Combinations

Compounded Compounded T3/T4 Combinations is dispensed under 503A on a patient-specific prescription. Depending on your role, the next step looks different.

FOR PRESCRIBING CLINICIANS

Offer this medication

A pharmacist will follow up within two business days. We'll cover state availability, supported formulations, and what integration looks like for your clinic.

ronanrx.com/request-partnership-call

PATIENT WITH A DOCTOR

Receive your prescription

If your doctor has prescribed Compounded T3/T4 Combinations, sign up so we can prepare and ship your medication. The signup wizard collects intake and connects you to the prescribing workflow.

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PATIENT WITHOUT A DOCTOR

Find a partner clinic

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Other compounds RonanRx makes

This monograph is one of many in the RonanRx formulary. Every compound below is prepared under 503A on a patient-specific prescription. Browse the full catalog at ronanrx.com/medications and ronanrx.com/peptides, or scan the codes at right for each index.

Medications

Peptides

MEDICATIONS (42)

Alpha-Lipoic Acid (ALA) — Antioxidant & mitochondrial
Coenzyme Q10 (CoQ10) — Antioxidant & mitochondrial
Glutathione — Antioxidant & mitochondrial
Methylene Blue — Antioxidant & mitochondrial
NAD+ / NMN — Antioxidant & mitochondrial
Compounded Topical Anesthetics (BLT, LET) — Dermatology
Topical Minoxidil — Dermatology
Topical Tretinoin — Dermatology
Compounded Magnesium — Energy & nutritional
Cyanocobalamin — Energy & nutritional
High-Dose Vitamin D — Energy & nutritional
Hydroxocobalamin — Energy & nutritional
Iron (Compounded) — Energy & nutritional
L-Carnitine — Energy & nutritional
Methylcobalamin (B12) — Energy & nutritional
Methylfolate — Energy & nutritional
Anastrozole — Hormone optimization
Clomiphene & Enclomiphene — Hormone optimization
DHEA — Hormone optimization
Estradiol — Hormone optimization
Estriol — Hormone optimization
Human Chorionic Gonadotropin (HCG) — Hormone optimization
Oxytocin — Hormone optimization
Pregnenolone — Hormone optimization
Progesterone — Hormone optimization
Testosterone — Hormone optimization
Compounded Metformin — Metabolic & weight
Compounded Semaglutide — Metabolic & weight
Compounded Tirzepatide — Metabolic & weight
Lipotropic Injection (MIC, MICC) — Metabolic & weight
Low-Dose Naltrexone (LDN) — Metabolic & weight
Naltrexone-Bupropion Combination — Metabolic & weight
Topiramate — Metabolic & weight
Bremelanotide / PT-141 — Sexual health
Compounded Sildenafil — Sexual health
Compounded Tadalafil — Sexual health
Trimix Injection — Sexual health
Compounded Gabapentin — Sleep & recovery
Compounded Melatonin — Sleep & recovery
Compounded T3 (Liothyronine) — Thyroid
Compounded T3/T4 Combinations — Thyroid
Compounded T4 (Levothyroxine) — Thyroid

PEPTIDES (21)

Sermorelin — Available now

Tesamorelin — Available now

AOD-9604 — Growth-hormone axis (under FDA review)

CJC-1295 — Growth-hormone axis (under FDA review)

GHRP-2 / GHRP-6 — Growth-hormone axis (under FDA review)

Hexarelin — Growth-hormone axis (under FDA review)

Ipamorelin — Growth-hormone axis (under FDA review)

MK-677 / Ibutamoren — Growth-hormone axis (under FDA review)

5-Amino 1MQ — Metabolic & longevity (under FDA review)

Epitalon / Epithalon — Metabolic & longevity (under FDA review)

MOTS-C — Metabolic & longevity (under FDA review)

Thymosin Alpha-1 / Thymalin — Metabolic & longevity (under FDA review)

DSIP, Delta Sleep-Inducing Peptide — Neuro & cognitive (under FDA review)

Selank — Neuro & cognitive (under FDA review)

Semax — Neuro & cognitive (under FDA review)

Vasoactive Intestinal Peptide (VIP) — Neuro & cognitive (under FDA review)

BPC-157 — Tissue repair (under FDA review)

KPV — Tissue repair (under FDA review)

LL-37 — Tissue repair (under FDA review)

Pentadeca Arginate (PDA) — Tissue repair (under FDA review)

TB-500 / Thymosin Beta-4 — Tissue repair (under FDA review)