CLINICAL MONOGRAPH · THYROID

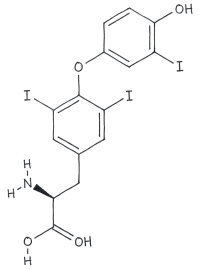
Compounded T3 (Liothyronine)

Active triiodothyronine for thyroid hormone replacement

T3 (liothyronine) is the active form of thyroid hormone, the molecule that actually does the work inside your cells. Most of the T3 in a healthy person is made inside the body by converting T4 (the storage form, levothyroxine) into T3 in tissues such as the liver, brain, and muscle. Standard hypothyroidism treatment uses T4 alone (Synthroid, Levoxyl, generic levothyroxine) because the body normally handles the T4-to-T3 conversion on its own [jonklaas2014_ata; celi2011; hennessey2015].

Some patients still feel unwell on T4 alone, fatigue, brain fog, low mood, even when their TSH lab is normal. Adding a small amount of T3 is one option clinicians consider in those cases. The FDA-approved T3 product in the United States is Cytomel (also available as generic liothyronine), made in 5, 25, and 50 mcg tablets [fda_label_cytomel].

RonanRx can compound liothyronine when the commercial tablets don't fit the prescription: as a sustained-release capsule (which spreads the T3 dose out across the day and avoids the early peak the immediate-release tablet produces), at fine custom strengths (like 1.25 or 2.5 mcg, smaller than the smallest commercial 5 mcg tablet), in an allergen-free or lactose-free form, or as a pediatric oral suspension. Compounded T3 is dispensed only on a doctor's prescription for a specific patient with a documented reason the commercial product won't work [fda503a].



EVIDENCE POSTURE FDA APPROVED WELL STUDIED REVIEWED **2026-05-11**

State-licensed 503A | Pharmacist reviewed | Doctor led | Cold-chain ready | Patient choice preserved

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FOR CLINICIANS

Liothyronine sodium is L-triiodothyronine, the bioactive thyroid hormone produced physiologically by 5'-deiodination of T4 by DIO1 (predominantly hepatic and renal) and DIO2 (predominantly central nervous system, pituitary, brown adipose tissue, and skeletal muscle) [bianco_dio2_review] [fda_label_cytomel]. Standard care for primary hypothyroidism is T4 monotherapy (levothyroxine), which the 2014 American Thyroid Association guideline endorses as first-line based on convenience, long half-life, and the assumption that peripheral conversion will produce physiologic intracellular T3 [jonklaas2014_ata]. The 2012 European Thyroid Association guideline allows a trial of T4+T3 combination therapy in patients with persistent symptoms despite biochemically euthyroid T4 monotherapy [wiersinga2012_eta]; the 2021 joint ATA/ETA/BTA consensus document reaffirms this conditional position [jonklaas2021_consensus].

Combination T4+T3 evidence: the Bunevicius 1999 NEJM crossover trial in 33 patients reported improved mood and neuropsychological function on partial T4-to-T3 substitution compared with T4 monotherapy [bunevicius1999], generating clinical interest [fda_label_cytomel]. Subsequent larger randomized trials, Walsh 2003 (n=110, Australia) [walsh2003], Clyde 2003 (JAMA, n=46) [clyde2003], Appelhof 2005 (n=141, two ratios) [appelhof2005], Nygaard 2009 (n=59) [nygaard2009], and Shakir 2021 (n=75, three-arm crossover) [shakir2021], did not show consistent improvements in quality of life, mood, or cognition on T4+T3 vs T4 alone in unselected hypothyroid populations. Meta-analyses by Grozinsky-Glasberg 2006 (eleven trials, n=1216) [grozinsky2006] and Ma 2009 (nine trials) [ma_combination_meta] found no overall benefit, although patient preference frequently favored combination therapy. The Panicker 2009 reanalysis of the Saravanan/Bunevicius datasets identified that carriers of the DIO2 Thr92Ala polymorphism reported greater symptomatic benefit from combination therapy [panicker2009_dio2], a finding that has not been prospectively replicated and that does not justify population-level genotyping but is the strongest available signal of a responder phenotype.

The intrinsic problem with manufactured Cytomel for combination therapy is pharmacokinetic: immediate-release liothyronine produces a Tmax at 2, 4 hours and a 30, 40% supraphysiologic peak in serum T3 even at replacement doses [celi2011]. Celi 2011 crossover-designed an experiment using thrice-daily liothyronine to attenuate this peak and reported preserved metabolic markers vs equivalent-dose levothyroxine [celi2011]. Compounded sustained-release liothyronine capsules, prepared with controlled-release excipients to spread absorption across 8, 24 hours, are the practical solution most clinicians use when prescribing combination therapy, and are one of the legitimate 503A roles for compounded T3 [hennessey2015] [fda_label_cytomel]. Other documented 503A roles are custom sub-5-mcg strengths for fine titration, allergen-free preparations (Cytomel's excipients include lactose, modified food starch, and calcium sulfate), and oral suspensions for pediatric or dysphagic patients.

Off-label use of T3 augmentation in major depressive disorder is supported by Aronson 1996 meta-analysis (eight trials) [aronson1996], Joffe 1993 (placebo-controlled vs lithium augmentation) [joffe1993], and Cooper-Kazaz 2007 (combined sertraline + T3 RCT) [cooper_kazaz2007]; the STAR*D level-3 trial reported approximately 25% remission for T3 augmentation, non-significantly different from lithium augmentation [nierenberg2006_stard]. Cardiovascular caveats: supraphysiologic serum T3 from immediate-release Cytomel transiently lowers TSH and increases sympathetic tone; chronically suppressed TSH is associated with atrial fibrillation in older adults [sawin_afib, surks2004, biondi_klein2004]. Klemperer 1995 NEJM reported short-term cardiac benefit when low-dose IV T3 was given as part of cardiopulmonary bypass protocols [klemperer1995]. Liothyronine is on the World Anti-Doping Agency prohibited list in some sport contexts [fda_label_cytomel].

Why Personalized Compounded T3 (Liothyronine)

Cytomel's approved strengths (5, 25, and 50 mcg immediate-release tablets) were set for the average adult athyreotic patient in the 1950s. They were not set for your residual thyroid function, your DIO2 genotype, your tolerance for the early serum-T3 peak that an immediate-release tablet produces at 2 to 4 hours, your reaction to lactose or modified food starch in the tablet binder, or the fact that your prescriber wants to add 1.25 mcg to your T4 regimen rather than the 5 mcg the smallest commercial tablet delivers. Combination T4+T3 therapy in particular runs into the pharmacokinetic problem that once-daily immediate-release liothyronine produces a 30 to 40 percent supraphysiologic peak that a healthy thyroid never generates.

That gap is what a compounding pharmacy fills. Liothyronine is the same FDA-reviewed molecule whether it is pressed into a 5 mcg Cytomel tablet or packed into a sustained-release capsule with a controlled-release excipient matrix designed to spread absorption across 8 to 24 hours. RonanRx can prepare custom strengths in 1.25, 2.5, or 7.5 mcg increments so a prescriber can titrate between the commercial doses, allergen-free or excipient-substituted capsules for patients who react to Cytomel's lactose, food starch, or calcium sulfate, and pediatric or adult oral suspensions for patients who cannot swallow a tablet. Each preparation requires a patient-specific prescription that documents the clinical reason the manufactured product does not fit.

Pharmacy did this work for a century before tablet manufacturing standardized everyone onto the same three doses. A clinician wrote the prescription, a pharmacist prepared it for the named patient, the bottle went home with that patient's name on it. Compounded T3 is that older arrangement, with state board inspection and 503A documentation keeping it honest.

Quick Facts About Compounded T3 (Liothyronine)

Category: Thyroid hormone (3,5,3'-triiodothyronine, T3); the active intracellular thyroid hormone produced by peripheral deiodination of T4

Active ingredient: Liothyronine sodium, synthetic L-triiodothyronine sodium salt, chemically identical to endogenous T3

FDA-approved branded products: Cytomel (liothyronine sodium tablets, 5/25/50 mcg) and generic liothyronine sodium tablets; Triostat (liothyronine sodium injection, 10 mcg/mL) for myxedema coma

Routes studied in humans: Oral (tablet, capsule, suspension), intravenous (Triostat); compounded sustained-release capsules and pediatric oral suspensions extend the route palette

Evidence posture: Liothyronine as part of replacement therapy is supported by the Bunevicius 1999 NEJM trial, multiple subsequent RCTs, the 2014 ATA hypothyroidism guidelines, the 2012 ETA combination-therapy guidelines, and the 2021 joint ATA/ETA/BTA consensus document. Meta-analyses do not show a consistent symptomatic advantage of T4+T3 over T4 alone in unselected hypothyroid populations; DIO2 polymorphism sub-analysis identifies a possible responder phenotype.

FDA-approval status: Manufactured Cytomel and generic liothyronine tablets are FDA-approved. Compounded liothyronine preparations (sustained-release capsules, custom-strength capsules, allergen-free, pediatric oral suspension) are not FDA-approved and are dispensed under 503A for documented patient-specific clinical needs that the manufactured tablets cannot meet.

Compounded under: 503A, patient-specific prescription only

Compounded role: Documented clinical needs the manufactured Cytomel/generic does not address: sustained-release capsules to attenuate the supraphysiologic peak that follows the immediate-release tablet (Cytomel's terminal half-life is approximately 24 hours but Tmax is 2, 4 hours, producing a marked early peak); custom strengths for fine titration in 1.25, 2.5, or 7.5 mcg increments below or between the commercial 5/25/50 mcg strengths; allergen-free or excipient-substituted preparations for patients reacting to Cytomel's lactose, modified food starch, or calcium sulfate excipients; oral suspensions for pediatric or dysphagic adults

Schedule: Not a controlled substance

Pregnancy: Replacement therapy for hypothyroidism is continued through pregnancy because untreated maternal hypothyroidism harms the fetus; thyroid hormone is not used for non-thyroid indications during pregnancy. Both Cytomel and generic liothyronine are not contraindicated in pregnancy when used for thyroid hormone replacement.

SPECIALS: PATIENT-SPECIFIC PRESCRIPTION ONLY

Compounded T3 (Liothyronine) 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 (Liothyronine)?

Triiodothyronine (T3; 3,5,3'-L-triiodothyronine) is the biologically active thyroid hormone. In humans, approximately 80% of circulating T3 is produced by extrathyroidal 5'-deiodination of T4 (thyroxine), with the remaining ~20% secreted directly by the thyroid gland. T3 binds nuclear thyroid hormone receptors (TRα, TRβ) and regulates transcription of genes governing basal metabolic rate, lipolysis, cardiac contractility, cerebral development, and many other processes [hennessey2015]. Liothyronine sodium is the synthetic L-enantiomer salt of T3, chemically identical to the endogenous hormone.

The FDA-approved manufactured liothyronine product is Cytomel (King Pharmaceuticals / Pfizer; originally approved in the 1950s), supplied as scored tablets at 5, 25, and 50 mcg strengths [fda_label_cytomel]. Generic liothyronine sodium tablets are also FDA-approved and widely available. Triostat is an FDA-approved injectable liothyronine product (10 mcg/mL) labeled for myxedema coma. Cytomel tablets contain lactose, modified food starch, calcium sulfate, gelatin, and other excipients; the excipient profile is a recurring driver of patient-specific compounding requests.

Compounded liothyronine preparations include sustained-release capsules (typically 5, 25 mcg per capsule with controlled-release matrices intended to extend the absorption profile across 8, 24 hours), immediate-release custom-strength capsules (1.25, 2.5, 7.5 mcg or other intermediates between commercial strengths), oral suspensions for pediatric or dysphagic use, and allergen-free or excipient-substituted versions [celi2011]. None of these compounded preparations are FDA-approved; each is dispensed on a patient-specific prescription that documents the clinical reason the manufactured Cytomel or generic tablets cannot meet the patient's need [hennessey2017_emergence].

How Compounded T3 (Liothyronine) Works

T4 (thyroxine) is the predominant hormone secreted by the thyroid gland, but T4 is essentially a prohormone. T4 is converted to T3, the biologically active hormone, by a family of selenoenzymes called iodothyronine deiodinases. Type 1 (DIO1) is expressed primarily in liver and kidney and contributes to

circulating T3. Type 2 (DIO2) is expressed in central nervous system, pituitary, brown adipose tissue, skeletal muscle, and placenta, and produces T3 for local intracellular use. Type 3 (DIO3) inactivates both T4 and T3 by inner-ring deiodination. Tissue-level T3 concentration is therefore controlled separately from circulating T3 [bianco_dio2_review].

Once produced, T3 enters cells via specific transporters (notably MCT8) and binds nuclear thyroid hormone receptors (TRα predominantly in heart, bone, and brain; TRβ predominantly in liver, kidney, and pituitary). The TR-T3 complex heterodimerizes with retinoid X receptor and regulates transcription of thyroid-hormone-response-element-containing genes. Net physiologic effects include increased basal metabolic rate, increased cardiac output (positive chronotropy and inotropy), enhanced lipolysis and hepatic cholesterol clearance, modulation of central catecholamine sensitivity, and, in development, neuronal migration and myelination.

Therapeutic implications: T4 monotherapy raises serum T4 and lets the patient's own deiodinase machinery convert it to T3. Most patients tolerate this fully, peripheral DIO1/DIO2 activity is sufficient to produce physiologic intracellular T3 [jonklaas2014_ata]. A subset of patients, including those with extensive thyroidectomy [gullo2011, ito2019, ito_atrophic], DIO2 polymorphism carriers [panicker2009_dio2], or other reasons for impaired conversion, may maintain low-normal serum free T3 on T4 monotherapy despite a normal TSH, and have been hypothesized to benefit from supplemental T3. Whether the clinical correlate of low serum FT3 in these patients translates into a treatable symptom remains contested across the trial literature [grozinsky2006, jonklaas2021_consensus].

Biological Role of Compounded T3 (Liothyronine)

Thyroid hormone, collectively T4 plus T3, with T3 the active intracellular ligand, regulates the 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) [jonklaas2014_ata] [aronson1996; cooper_kazaz2007]. Thyroid hormone excess produces hyperthyroidism (palpitations, atrial fibrillation, heat intolerance, weight loss, tremor, anxiety, osteoporosis). During fetal and neonatal life, thyroid hormone is essential for normal CNS development; iodine-deficient endemic cretinism remains a significant cause of preventable intellectual disability worldwide [nierenberg2006_stard].

T3 specifically is the molecule that occupies the nuclear thyroid hormone receptor [jonklaas2014_ata]. T4 has roughly one-tenth the affinity for TR and is essentially a prohormone. The clinical reason T4 (levothyroxine) is standard replacement therapy, rather than T3 itself, is that T4's long serum half-life (~7 days) produces stable circulating levels that the body's deiodinase machinery converts to T3 as needed at tissue level, mimicking the homeostatic role of the gland. T3, with its 1-day half-life and rapid receptor occupancy, is more pharmacologically active but harder to dose to physiologic levels.

Beyond replacement therapy, T3 has been explored in major depressive disorder augmentation [joffe1993], in cardiovascular surgery [klemperer1995] [klemperer1995], and in low-T3 syndrome of critical illness (a non-thyroidal illness state in which serum T3 falls with systemic illness; routine T3 supplementation has not shown mortality benefit and is not standard of care) [jonklaas2014_ata]. Off-label use for weight loss and athletic performance is not evidence-supported, is associated with cardiovascular harm, and is prohibited by the World Anti-Doping Agency in many sport contexts.

Detailed Mechanism of Compounded T3 (Liothyronine)

Deiodinase enzymology. The three iodothyronine deiodinases are selenocysteine-containing enzymes that catalyze monoiodination of the thyroid hormone iodothyronine ring. DIO1 is a low-affinity, high-capacity enzyme expressed in liver, kidney, and thyroid that catalyzes both inner-ring (5) and outer-ring (5') deiodination; its kinetics are sensitive to propylthiouracil. DIO2 is a high-affinity, low-capacity outer-ring (5') deiodinase expressed in CNS, pituitary, brown adipose tissue, skeletal muscle, and placenta; DIO2 is regulated post-translationally by ubiquitination linked to thyroid hormone status. DIO3 is an inner-ring deiodinase that inactivates T4 and T3; it is highly expressed in fetal tissues, placenta, and certain pathologic settings (Bianco review) [bianco_dio2_review]. The relative contribution of DIO1 versus DIO2 to circulating T3 has been progressively reframed, current evidence suggests DIO2 may contribute a larger share than the historical DIO1-centric model proposed.

Polymorphisms and individual variation. The DIO2 Thr92Ala polymorphism (rs225014) is a common variant in the DIO2 gene with allele frequency approximately 30, 40% in populations of European ancestry. Panicker and colleagues (2009 JCEM) 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 T4+T3 than non-carriers [panicker2009_dio2]. The earlier Appelhof 2005 analysis using a different dataset and outcome panel had not shown an association of DIO2 polymorphisms with well-being or preference [appelhof2005_dio2]. The clinical inference, that DIO2 genotype identifies a responder phenotype to combination therapy, is biologically plausible (homozygotes have reduced local T3 generation in DIO2-expressing tissues such as the brain) but has not been prospectively replicated in a powered trial. Population genotyping is not currently recommended by ATA, ETA, or the 2021 joint consensus [jonklaas2014_ata, wiersinga2012_eta, jonklaas2021_consensus].

Pharmacokinetic basis for combination-therapy difficulty. Native circulating T3 has a serum half-life of approximately 1 day in euthyroid adults. Oral immediate-release liothyronine has a Tmax of 2, 4 hours and produces a 30, 40% above-baseline peak in serum T3 within the first 4, 6 hours after dosing [celi2011]. Even at replacement doses (10, 15 mcg/day for an athyreotic adult, or smaller add-on doses to T4 monotherapy), the once-daily immediate-release tablet does not reproduce the steady serum T3 of a healthy gland. Celi 2011 used a thrice-daily dosing schedule in a randomized crossover to flatten the peak-trough excursion and compared metabolic markers (resting energy expenditure, lipid panel, body weight) to

weight-equivalent levothyroxine; the cross-over showed comparable TSH suppression but improvement in lipid markers on liothyronine, suggesting that the pharmacokinetic-flattening approach is mechanistically reasonable [celi2011]. Compounded sustained-release liothyronine is the alternative pharmacokinetic-flattening strategy, controlled-release excipients designed to extend the absorption window across the dosing interval, producing lower peaks and more sustained levels.

Conversion impairment in athyreotic patients. Gullo and colleagues (2011 PLoS One) measured serum FT3 and FT3/FT4 ratios in 1811 athyreotic patients on L-T4 monotherapy compared with 3875 euthyroid controls; athyreotic patients had significantly lower FT3 and FT3/FT4 ratio at any given TSH, suggesting that L-T4 monotherapy does not fully normalize peripheral T3 in patients without a thyroid gland [gullo2011]. Ito and colleagues (2019 Thyroid; 2019 Endocrine Journal) reported similar findings in post-radioiodine Graves disease and post-thyroidectomy populations, with a subset of patients experiencing residual hypothyroid symptoms despite a TSH in the reference range and low-normal FT3 [ito2019, ito_atrophic]. These observations underpin the clinical interest in supplemental T3 for athyreotic patients, even though prospective trials of routine combination therapy in this population have not shown consistent symptom benefit.

Central regulation and the HPT feedback loop. Hypothalamic TRH stimulates pituitary TSH; TSH stimulates thyroid hormone synthesis and secretion. T3 (produced locally in the pituitary by DIO2 from circulating T4) is the dominant feedback signal that suppresses TSH. Because immediate-release liothyronine produces post-dose serum T3 peaks, TSH suppression is brisk and TSH is no longer a reliable indicator of overall thyroid hormone adequacy during the dosing interval. Clinicians using combination therapy commonly target TSH in the lower half of the reference range and supplement with FT3 measurement; trough FT3 is preferred when feasible. Hoermann and colleagues (2015 Front Endocrinol) modeled the homeostatic deviations of the HPT axis under L-T4 monotherapy and combination regimens and noted that TSH-only targeting can leave a meaningful subset of patients with discordant FT3 status [hoermann2015].

Compounded T3 (Liothyronine) Research History

Thyroid hormone replacement traces to the 1890s, when George Murray demonstrated that injectable sheep-thyroid extract reversed myxedema. Desiccated thyroid extract (porcine, containing both T4 and T3 in approximately 4:1 ratio) was the only available thyroid replacement through the first half of the twentieth century. Synthetic levothyroxine (L-T4) became commercially available in the 1950s and progressively displaced desiccated thyroid as the standard of care, supported by the recognition that the long T4 half-life produced more reproducible serum levels and that peripheral deiodination would supply tissue T3 [hennessey2017_emergence].

Liothyronine sodium (synthetic L-T3) was characterized and entered clinical use in the 1950s. Cytomel was FDA-approved in 1956 [fda_label_cytomel]. The early clinical role of T3 was niche: rapid pre-radioiodine

TSH suppression, treatment of myxedema coma (intravenous Triostat), and short-term replacement during thyroid hormone withdrawal for thyroid cancer follow-up imaging. Routine combination of T4 and T3 for chronic hypothyroidism was discouraged through the 1960s, 1990s on the grounds that peripheral conversion supplied tissue T3 adequately.

The modern combination-therapy debate began with Bunevicius and colleagues' 1999 NEJM trial [bunevicius1999], a 33-patient crossover that substituted 12.5 mcg of T3 for 50 mcg of T4 in standard L-T4 regimens and reported improved mood and cognitive performance on the T4+T3 arm. This finding was followed by larger replication attempts that were predominantly null: Walsh 2003 (n=110) [walsh2003], Clyde 2003 (JAMA, n=46) [clyde2003], Saravanan/Appelhof series 2005 (n=141; multiple ratios) [appelhof2005], Nygaard 2009 (n=59) [nygaard2009], and Shakir 2021 (n=75 crossover comparing L-T4, desiccated thyroid extract, and L-T4 + L-T3) [shakir2021]. The Grozinsky-Glasberg 2006 JCEM meta-analysis of 11 trials (n=1216) [grozinsky2006] and the Ma 2009 meta-analysis of 9 trials [ma_combination_meta] concluded no consistent benefit of combination therapy on quality of life, mood, or cognition, although patient preference often favored combination therapy in crossover designs.

Mechanistic interest in a responder phenotype emerged with the Panicker 2009 JCEM reanalysis [panicker2009_dio2] of the Saravanan and Bunevicius datasets, which identified the DIO2 Thr92Ala polymorphism as a candidate moderator. The Appelhof 2005 JCEM analysis of a different dataset had not found such an association [appelhof2005_dio2]. The Hoang 2013 JCEM randomized crossover compared desiccated thyroid extract with L-T4 and reported a patient-preference signal favoring desiccated thyroid [hoang2013]. The Celi 2011 JCEM randomized crossover of L-T3 monotherapy (thrice daily) versus L-T4 reported comparable TSH suppression but improvement in lipid markers on the L-T3 arm [celi2011], generating interest in physiologic-PK approaches to T3 dosing.

Athyreotic patients have received particular research attention. Gullo and colleagues' 2011 PLoS One analysis (n=1811 athyreotic, n=3875 euthyroid controls) [gullo2011] demonstrated lower FT3 and FT3/FT4 ratio in L-T4-monotherapy-treated patients without a gland. Ito and colleagues confirmed this in post-thyroidectomy and post-radioiodine populations [ito2019, ito_atrophic]. McAninch and Bianco (2015 Lancet Diabetes & Endocrinology) [mcaninch2015] integrated these strands into a unifying view that L-T4 monotherapy is sufficient for most hypothyroid patients but leaves a subset with biochemically detectable peripheral T3 deficit and persistent symptoms. Ettleson and Bianco (2020 JCEM) [ettleson_bianco] surveyed the unmet-need landscape and recommended a low-dose trial of combination therapy in selected patients, with the 2021 ATA/ETA/BTA joint consensus document [jonklaas2021_consensus] codifying a conditional, individualized approach.

The compounded sustained-release liothyronine literature is comparatively small. Multiple regional series and pharmacy-led case reports describe sustained-release liothyronine capsule preparations across 5, 25 mcg per capsule. Hennessey's review [hennessey2015] catalogs sustained-release liothyronine and other compounded options as legitimate alternatives where the immediate-release commercial tablet does not match the clinical objective. The general clinical principle motivating sustained-release compounding is the

pharmacokinetic mismatch documented by Celi 2011, immediate-release liothyronine produces post-dose supraphysiologic T3 peaks that the body of a healthy gland does not produce.

Compounded T3 (Liothyronine) Timeline

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

1950s • Synthetic levothyroxine (L-T4) enters clinical practice and progressively replaces desiccated thyroid extract as standard hypothyroidism therapy [hennessey2017_emergence]

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

1993 • Joffe et al [joffe1993]. (Arch Gen Psychiatry) report placebo-controlled efficacy of T3 augmentation of tricyclic antidepressants in refractory unipolar depression

1995 • Klemperer et al [klemperer1995]. (NEJM) report that low-dose IV T3 during coronary-artery bypass surgery improves post-bypass cardiac index

1995 • Escobar-Morreale et al [escobar_morreale_rat]. (J Clin Invest) demonstrate in thyroidectomized rats that L-T4 monotherapy does not normalize tissue T3 in all organs, mechanistic foundation for combination-therapy interest

1996 • Aronson et al [aronson1996]. (Arch Gen Psychiatry) meta-analyze eight controlled trials of T3 augmentation in refractory depression

1999 • Bunevicius et al [bunevicius1999]. (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 and Prange (Endocrine) repeat the comparison in post-thyroidectomy Graves disease patients [bunevicius2002]

2003 • Walsh et al [walsh2003]. (JCEM) and Clyde et al [clyde2003]. (JAMA) publish larger combination-therapy trials with predominantly null primary outcomes

2004 • Sawin (Thyroid) and Biondi & Klein (Endocrine) catalog atrial-fibrillation and cardiovascular risk of subclinical hyperthyroidism, relevant to T3 dosing pharmacology [sawin_afib; biondi_klein2004]

2004 • Surks et al [surks2004]. (JAMA) publish AACE/ATA/Endocrine Society consensus review on subclinical thyroid disease

2005 • Appelhof et al [appelhof2005; appelhof2005_dio2]. (JCEM) compare two T4:T3 dose ratios with T4 monotherapy in 141 patients, null primary outcome; companion DIO2 polymorphism analysis also null

2006 • Grozinsky-Glasberg et al [grozinsky2006]. (JCEM) meta-analyze 11 combination-therapy trials (n=1216), no consistent advantage on quality of life or mood

2006 • Nierenberg et al [nierenberg2006_stard]. (Am J Psychiatry) report the STAR*D level-3 comparison of T3 augmentation vs lithium augmentation after two failed antidepressant trials, comparable remission rates

2007 • Cooper-Kazaz et al [cooper_kazaz2007]. (Arch Gen Psychiatry) RCT of sertraline + T3 vs sertraline alone, combined treatment superior on depression scales

2008 • Biondi & Cooper (Endocr Rev) publish authoritative review of subclinical thyroid dysfunction including the cardiovascular implications of suppressed TSH [biondi_cooper2008]

2009 • Panicker et al [panicker2009_dio2]. (JCEM) reanalyze Saravanan/Bunevicius datasets and identify DIO2 Thr92Ala polymorphism as a candidate moderator of combination-therapy response

2009 • Ma et al. (Nucl Med Commun) and Nygaard et al [ma_combination_meta; nygaard2009]. (Eur J Endocrinol) add to the meta-analytic and trial datasets on combination therapy

2010 • Flynn et al [flynn2010]. (JCEM) report that suppressed serum TSH in long-term thyroxine-treated patients is associated with cardiovascular morbidity and fractures

2011 • Celi et al [celi2011]. (JCEM) crossover trial of thrice-daily L-T3 vs equivalent-dose L-T4, comparable TSH suppression, improvement in lipid markers on the L-T3 arm

2011 • Gullo et al [gullo2011]. (PLoS One) demonstrate that athyreotic patients on L-T4 monotherapy have lower FT3 and FT3/FT4 ratio than euthyroid controls at any given TSH

2012 • Wiersinga et al [wiersinga2012_eta]. publish ETA guidelines on the use of L-T4 + L-T3 in hypothyroidism, conditional position permitting a trial of combination therapy in symptomatic patients

2012 • Biondi & Wartofsky (JCEM) review combination treatment with T4 and T3, toward personalized replacement [biondi2012]

2013 • Hoang et al [hoang2013]. (JCEM) randomized crossover compares desiccated thyroid extract with L-T4, patient preference favored desiccated thyroid

2014 • Jonklaas et al [jonklaas2014_ata]. 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 use; Hoermann et al [hennessey2015; hoermann2015]. (Front Endocrinol) model HPT axis homeostasis under monotherapy

2015 • McAninch & Bianco (Lancet Diabetes Endocrinol) review the variable effectiveness of levothyroxine monotherapy, integrating clinical, biochemical, and genetic strands [mcaninch2015]

2017 • Hennessey (Endocrine) historical review of the emergence of levothyroxine as the standard thyroid replacement therapy [hennessey2017_emergence]

2017 • Gullo et al [gullo2017]. (Clin Endocrinol) report seasonal variations in TSH in athyreotic patients on L-T4 monotherapy

2018 • Dayan & Panicker (Thyroid Res) review management of hypothyroidism with combination T4+T3 in clinical practice [dayan_panicker]

2019 • Ito et al [ito2019; ito_atrophic]. (Thyroid; Endocr J) report low serum FT3 and residual hypothyroid symptoms in athyreotic patients on L-T4 monotherapy

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

2021 • Jonklaas, Bianco, Cappola et al [jonklaas2021_consensus]. publish joint ATA / ETA / BTA consensus document on the evidence-based use of L-T4/L-T3 combinations

2021 • Shakir et al [shakir2021]. (JCEM) three-arm crossover comparison of L-T4, desiccated thyroid extract, and L-T4 + L-T3

2021 • Perros et al [perros2021]. (Eur J Endocrinol) report risk-of-death-based therapeutic targets for levothyroxine-treated primary hypothyroidism

Clinical Contexts for Compounded T3 (Liothyronine)

Primary hypothyroidism, supplementary T3 in addition to L-T4 monotherapy

FDA APPROVED

FDA-approved indication for manufactured Cytomel / generic liothyronine: as a component of thyroid hormone replacement therapy. Combination therapy is not routinely recommended by the 2014 ATA guideline but is permitted as a trial in selected patients with persistent symptoms despite biochemical euthyroidism on L-T4 monotherapy.

Liothyronine (Cytomel) is FDA-approved as replacement or supplemental therapy in hypothyroidism of any etiology, except transient hypothyroidism during the recovery phase of subacute thyroiditis [fda_label_cytomel] [bunevicius1999]. In practice the dominant standard of care is L-T4 monotherapy [jonklaas2014_ata]. The 2012 ETA guideline [wiersinga2012_eta] and the 2021 joint ATA/ETA/BTA consensus [jonklaas2021_consensus] allow a trial of combination L-T4 + L-T3 in patients with persistent symptoms despite a normal TSH on monotherapy. Meta-analytic evidence [grozinsky2006, ma_combination_meta] does not show a consistent advantage of combination over monotherapy in unselected populations, although patient preference frequently favors combination in crossover designs. DIO2 polymorphism reanalysis [panicker2009_dio2] suggests a responder phenotype but has not been prospectively replicated. Athyreotic patients (post-thyroidectomy, post-radioiodine) have measurably lower FT3 on L-T4 monotherapy [gullo2011, ito2019] and are a subgroup in which combination therapy is most often considered.

Branded product: Cytomel (liothyronine sodium, Pfizer) and generic liothyronine sodium tablets

Pre-radioiodine TSH suppression in thyroid cancer protocols FDA APPROVED

FDA-approved as a component of thyroid hormone replacement; commonly used short-term in pre-radioiodine and thyroid hormone withdrawal protocols because its shorter half-life allows faster TSH rise after discontinuation than L-T4 withdrawal.

Liothyronine is FDA-labeled for use as a replacement / supplemental thyroid hormone [fda_label_cytomel] [jonklaas2014_ata]. A specific clinical role exploits T3's short half-life: in patients preparing for radioiodine ablation or whole-body iodine scanning, liothyronine can be substituted for L-T4 for a period (typically 4 weeks), then discontinued, allowing TSH to rise to scan-appropriate levels in ~2 weeks rather than the 4, 6 weeks required after L-T4 withdrawal. This shortens the symptomatic hypothyroid window for the patient.

Branded product: Cytomel and generic liothyronine sodium tablets

Myxedema coma, intravenous liothyronine FDA APPROVED

FDA-approved indication for manufactured Triostat (intravenous liothyronine).

Triostat (liothyronine sodium injection, 10 mcg/mL) is FDA-approved for myxedema coma, an endocrine emergency characterized by severe hypothyroidism, hypothermia, and depressed consciousness [fda_label_cytomel; jonklaas2014_ata]. Combined IV T4 and T3 (or IV T4 with adjunctive low-dose IV T3) plus supportive care and stress-dose glucocorticoid is the standard inpatient approach.

Branded product: Triostat (liothyronine sodium injection, JHP Pharmaceuticals)

Major depressive disorder, antidepressant augmentation WELL STUDIED

Off-label use studied in multiple controlled trials and meta-analyses; not a labeled indication.

Triiodothyronine has been studied as an augmentation strategy in major depressive disorder partially responsive or unresponsive to standard antidepressants. The Aronson 1996 meta-analysis of eight controlled trials [aronson1996] reported a small but significant augmentation effect. Joffe 1993 (Arch Gen Psychiatry) [joffe1993] randomized refractory unipolar depression to T3 vs lithium vs placebo augmentation of tricyclic antidepressants, with both active arms superior to placebo. Cooper-Kazaz 2007 (Arch Gen Psychiatry) [cooper_kazaz2007] reported that combined sertraline + T3 from treatment initiation was superior to sertraline alone on depression outcomes. The STAR*D level-3 trial [nierenberg2006_stard] compared T3 with lithium augmentation after two failed antidepressant trials; remission rates were approximately 25% in each arm with no statistically significant difference, and T3 was better tolerated. Long-term durability of benefit is limited, and current depression-treatment guidelines list T3 augmentation as one of several second- or third-line strategies.

Cardiopulmonary bypass surgery, short-term low-dose IV T3 WELL STUDIED

Studied in randomized trials in cardiac surgery; not an FDA-labeled indication for routine use.

Klemperer and colleagues (1995 NEJM) [klemperer1995] randomized patients undergoing coronary artery bypass surgery to receive low-dose IV T3 or placebo at the start of cardiopulmonary bypass and reported improved cardiac index and reduced inotrope requirement post-bypass. Subsequent trials have generally supported a short-term hemodynamic effect of IV T3 in this context, although routine use varies by surgical program. This is a hospital-administered IV protocol and is not a context relevant to outpatient compounded T3 dispensing.

Bipolar disorder, adjunctive therapy EMERGING

Off-label; studied in small open-label series and a few randomized trials, predominantly for rapid-cycling bipolar disorder.

Supraphysiologic T4 and supplemental T3 have been studied in rapid-cycling bipolar disorder and in bipolar depression that is partially responsive to standard mood stabilizers. The evidence base is smaller than for unipolar depression augmentation and consists mainly of open-label series and a few small randomized trials [aronson1996; joffe1993]. Use is highly individualized and is typically managed within a psychiatry-endocrinology collaboration.

Off-Label Uses of Compounded T3 (Liothyronine)

T3 augmentation in major depressive disorder WELL STUDIED

*Off-label; supported by Joffe, Aronson meta-analysis, Cooper-Kazaz, and the STAR*D level-3 result. Long-term durability of benefit limited.*

See clinical_contexts [nierenberg2006_stard]. Off-label augmentation strategy with controlled-trial support [joffe1993; aronson1996; cooper_kazaz2007].

Bipolar disorder maintenance EMERGING

Off-label; small open-label and randomized trials, predominantly in rapid-cycling.

Adjunctive supraphysiologic or low-dose T3 in rapid-cycling bipolar disorder, evidence is limited and use is highly individualized within psychiatry-endocrinology collaboration [aronson1996].

FDA-Approved Uses of Compounded T3 (Liothyronine)

Brand	Indication	Year	Route
Cytomel	Replacement or supplemental therapy in hypothyroidism of any etiology, except transient hypothyroidism during the recovery phase of subacute thyroiditis; TSH suppression in management of thyroid cancer; diagnostic agent in suppression tests to differentiate suspected mild hyperthyroidism or thyroid gland autonomy	1956	Oral tablet (5, 25, 50 mcg)
Generic liothyronine sodium tablets	Same as Cytomel, replacement or supplemental thyroid hormone	—	Oral tablet (5, 25, 50 mcg)
Triostat	Myxedema coma / precoma	—	

Brand	Indication	Year	Route
			Intravenous injection (10 mcg/mL)

The FDA-approved manufactured forms of liothyronine are Cytomel and generic liothyronine sodium tablets at 5, 25, and 50 mcg strengths, and Triostat injectable liothyronine 10 mcg/mL. Cytomel and the generic are labeled as replacement or supplemental thyroid hormone for hypothyroidism of any etiology (except subacute-thyroiditis recovery phase), for TSH suppression in thyroid cancer management, and as a diagnostic agent in suppression testing [fda_label_cytomel] [jonklaas2014_ata].

Thyroid hormones are not FDA-approved for the treatment of obesity. The Cytomel label carries language stating that the use of thyroid hormones for the treatment of obesity, alone or combined with other drugs, is unjustified and may be hazardous [fda_label_cytomel] [jonklaas2014_ata]. This warning context is well established in clinical practice and is the basis of cautious prescribing in patients without documented thyroid disease.

Compounded Compounded T3 (Liothyronine) (503A)

Compounded liothyronine occupies a clearly defined 503A niche that is distinct from typical 'essentially-a-copy' compounding territory. Cytomel and generic liothyronine are widely available, low-cost, and FDA-approved. RonanRx compounds liothyronine only when the prescribing clinician documents a patient-specific clinical need that the manufactured tablets cannot meet [fda503a, fda_essentially_a_copy] [fda_label_cytomel]. Four well-recognized 503A indications drive the great majority of compounded liothyronine prescriptions.

Sustained-release liothyronine capsules are the most clinically substantial compounded T3 use. Immediate-release Cytomel has Tmax 2, 4 hours and produces a 30, 40% above-baseline post-dose peak in serum T3 [celi2011]. This peak is non-physiologic, a healthy thyroid gland and intact peripheral deiodination produce steadier serum T3 [hennessey2015]. Sustained-release compounded capsules, prepared with controlled-release excipients designed to extend absorption across 8, 24 hours, are used in combination therapy regimens where the clinical aim is to add a small physiologic-amplitude T3 component to L-T4 monotherapy without producing the supraphysiologic peak that the immediate-release tablet creates. The 2021 ATA/ETA/BTA consensus document [jonklaas2021_consensus] notes that the pharmacokinetic profile of immediate-release liothyronine is suboptimal for steady physiologic replacement and recognizes sustained-release preparations as a clinically reasonable approach.

Custom strengths below or between the commercial 5/25/50 mcg increments are the second well-recognized compounded T3 indication. Cytomel's smallest commercial tablet is 5 mcg [fda_label_cytomel]. Many combination-therapy regimens require lower doses (1.25, 2.5, 3.75 mcg) and many patients require

titration steps smaller than the gap between commercial strengths. Splitting a 5 mcg scored tablet to 2.5 mcg is feasible but accuracy of split-tablet dosing is operator-dependent. Compounded custom-strength capsules deliver gravimetrically verified content at the prescribed dose.

Allergen-free and excipient-substituted preparations are a recurring compounding indication. Cytomel and most generic liothyronine tablets contain lactose, modified food starch, calcium sulfate, gelatin, and other excipients [fda_label_cytomel]. Patients with documented sensitivity to one of these excipients, most commonly lactose intolerance or gluten sensitivity (modified food starch is typically corn-derived but cross-contamination concerns exist), can be served with compounded lactose-free, corn-free, or specifically excipient-substituted capsules.

Pediatric oral suspensions and dysphagic-adult oral suspensions are the fourth recognized indication. No manufactured liquid liothyronine is available in the United States [fda_label_cytomel]. Compounded oral suspensions allow weight-based dosing in children and easier administration in adults with swallowing difficulty, with documented stability per the pharmacy's beyond-use-dating study or established literature.

Outside these patient-specific clinical needs, compounding of liothyronine is not appropriate under 503A. Routine substitution of compounded immediate-release liothyronine for Cytomel without a documented clinical reason does not satisfy the 'patient-specific clinical need' threshold under FDA's essentially-a-copy framework [fda_essentially_a_copy] [fda_label_cytomel]. RonanRx does not fill compounded T3 prescriptions on a preference- or price-only basis.

Compounded T3 (Liothyronine) Formulations and Routes

Form	Concentration	Description
Manufactured immediate-release oral tablet (reference product)	5, 25, 50 mcg	Cytomel (Pfizer) and generic liothyronine sodium tablets. Immediate-release. Tmax 2, 4 hours after oral administration; supraphysiologic post-dose peak in serum T3.
Manufactured intravenous liothyronine (reference product)	10 mcg/mL	Triostat, FDA-approved injectable liothyronine for myxedema coma. Inpatient use only.
Compounded sustained-release liothyronine capsule	Custom, typical 5 to 25 mcg per capsule	Capsule prepared with controlled-release excipients (e.g., hydrophilic matrix or coated bead) designed to extend absorption across 8, 24 hours and attenuate the post-dose peak characteristic of immediate-release tablets. Used in combination therapy regimens where physiologic-amplitude steady T3 is the clinical aim. Stability and release profile are documented per the pharmacy's product-specific data.

Form	Concentration	Description
Compounded immediate-release custom-strength capsule	Custom, typical 1.25, 2.5, 3.75, or 7.5 mcg per capsule	Capsule at a strength below or between the commercial 5/25/50 mcg increments. Used when the clinical regimen requires fine titration steps that the manufactured tablets do not provide.
Compounded allergen-free or excipient-substituted capsule	Matches commercial or custom strength	Capsule prepared without lactose, corn-derived starch, gluten-cross-contaminated excipients, or other excipients to which the patient has documented sensitivity.
Compounded oral suspension	Typical 5 mcg/mL or 10 mcg/mL	Liquid preparation for pediatric or dysphagic adult patients. Stability and beyond-use date assigned per the pharmacy's product-specific stability data.

Routes used in published literature: oral.

Compounded T3 (Liothyronine) Dosing

Route	Population	Range	Duration	Study type
Oral (immediate-release Cytomel, adult replacement)	Adults with hypothyroidism, Cytomel labeled regimen	Initial 25 mcg daily; increase by 12.5, 25 mcg every 1, 2 weeks based on TSH and clinical response; usual maintenance 25, 75 mcg daily. Initial dose in elderly or cardiac-disease patients should be 5 mcg daily with slower titration.	Indefinite while clinically beneficial	FDA-approved labeled regimen
Oral (immediate-release liothyronine, combination therapy add-on)	Adults on L-T4 monotherapy with persistent symptoms, considered for a combination-therapy trial per ATA/ETA/BTA consensus	Typical clinical practice: add 5, 12.5 mcg daily of liothyronine to a reduced L-T4 dose, with TSH and clinical reassessment at 6, 8 weeks. The 2021 consensus document recommends an L-T4:L-T3 dose ratio in the range of 13:1 to 20:1 by	Trial period of 3, 6 months; continue only if clear symptomatic benefit	Joint ATA/ETA/BTA consensus document; published RCT regimens (Bunevicius 1999, Walsh 2003, Appelhof 2005, Nygaard 2009, Shakir 2021)

Route	Population	Range	Duration	Study type
		weight as a starting point.		
Oral (compounded sustained-release liothyronine capsule)	Adults on L-T4 monotherapy with persistent symptoms, considered for combination-therapy trial where the clinical aim is to avoid the post-dose serum T3 peak of immediate-release liothyronine	Typical regimen: 5, 15 mcg sustained-release capsule once daily, added to a reduced L-T4 dose. Specific compounded SR product, strength, and dosing interval are individualized to the prescription.	Trial period of 3, 6 months; continue only if clear symptomatic benefit	Mechanistic rationale from Celi 2011 PK analysis; sustained-release approach catalogued by Hennessey 2015; clinical use is per individualized prescriber judgment
Oral (custom low-dose strengths)	Adults requiring titration steps smaller than the commercial 5 mcg minimum	Typical compounded strengths: 1.25, 2.5, 3.75, 7.5 mcg per capsule, dosed once daily or in divided doses per prescription	Indefinite while clinically beneficial	Individualized prescribing; no formal trial-defined regimen at sub-5-mcg strengths
Oral (T3 augmentation in major depressive disorder)	Adults with major depressive disorder partially or unresponsive to standard antidepressant therapy	Studied range: 25, 50 mcg daily of immediate-release liothyronine added to the antidepressant regimen for 3, 8 weeks; clinical reassessment for response; many protocols use 25 mcg daily as the starting dose	Off-label augmentation; duration of continuation contingent on response	Joffe 1993 RCT; Aronson 1996 meta-analysis; Cooper-Kazaz 2007 RCT; STAR*D level-3 (Nierenberg 2006)
Oral (pediatric replacement, Cytomel labeled)	Pediatric hypothyroidism	Per Cytomel pediatric labeling, with dose titrated by age, weight, and TSH; in practice, L-T4 monotherapy is the preferred first-line pediatric replacement, and pediatric use of liothyronine is generally limited to specific scenarios under	Indefinite while clinically beneficial	FDA-approved labeled regimen

Route	Population	Range	Duration	Study type
		endocrinology supervision		

Doses listed reflect the FDA-approved labeled regimens for Cytomel and the published clinical-trial regimens for off-label combination therapy and depression augmentation. They are not RonanRx prescribing recommendations. The prescribing clinician selects the formulation, strength, and dosing schedule based on the patient's clinical context, etiology of hypothyroidism (athyreotic vs intrinsic), age, cardiovascular status, prior tolerability of immediate-release Cytomel, and the goal of therapy [fda_label_cytomel].

Combination therapy is not first-line for most hypothyroid patients [fda_label_cytomel]. The 2014 ATA guideline [jonklaas2014_ata] recommends L-T4 monotherapy as the preferred replacement; the 2012 ETA guideline [wiersinga2012_eta] and the 2021 ATA/ETA/BTA consensus document [jonklaas2021_consensus] permit a 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.

When immediate-release liothyronine is used, divided dosing (twice or thrice daily) attenuates the post-dose peak compared with once-daily administration [celi2011] [fda_label_cytomel]. Sustained-release compounded capsules are the alternative pharmacokinetic-smoothing strategy and are clinically reasonable when the prescriber and pharmacy can document the product's release profile and beyond-use dating.

Cardiac-disease and elderly patients should start at the lowest available dose (5 mcg daily of immediate-release Cytomel, or smaller compounded strength) with slow titration [fda_label_cytomel]. Suppressed TSH on chronic therapy is associated with atrial fibrillation and fracture risk [flynn2010, surks2004, biondi_klein2004]; combination-therapy regimens should not be allowed to drift into a chronically suppressed TSH unless TSH suppression is the explicit goal (e.g., post-thyroidectomy thyroid cancer protocol).

Compounded T3 (Liothyronine) Safety

Liothyronine 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 supraphysiologic post-dose peak after immediate-release Cytomel [7] can produce transient palpitations and adrenergic symptoms even at appropriate replacement doses, particularly with once-daily dosing schedules. Dividing the daily dose or moving to a sustained-release compounded capsule attenuates this peak.

Cardiovascular safety is the principal organ-system concern. Long-term suppressed serum TSH in thyroid-hormone-treated patients is associated with atrial fibrillation [35][36] and increased cardiovascular morbidity and fracture risk [34]. Biondi and Klein (2004) reviewed the cardiovascular consequences of overt and subclinical hyperthyroidism [33]. Patients with established ischemic heart disease should start at the lowest available dose with slow titration; angina or arrhythmia precipitation is the most concerning short-term adverse event. Klemperer 1995 NEJM [21] established a short-term cardiac role for low-dose IV T3 during cardiopulmonary bypass but this is a separate clinical context from outpatient oral T3 therapy.

Bone health is affected by chronic over-replacement: suppressed TSH and elevated free T3 accelerate bone turnover and are associated with reduced bone mineral density and increased fracture risk in postmenopausal women and older men [34]. Routine DEXA monitoring is not standard practice for hypothyroid patients on appropriate replacement, but bone health is a consideration when TSH is chronically suppressed.

Thyroid hormones are not appropriate therapy for obesity. The Cytomel label carries language stating that use of thyroid hormones for treatment of obesity, alone or combined with other drugs, is unjustified and may be hazardous [41]. The combination of thyroid hormone and sympathomimetic amines (a historical 'rainbow diet pill' pattern) was associated with serious cardiovascular harm and is contraindicated.

Compounded liothyronine preparations are not FDA-approved and have not undergone the bioavailability, stability, and labeling review that the manufactured Cytomel and Triostat have. Compounded sustained-release liothyronine in particular has a release profile that depends on the formulation excipients and process; documented stability data and product-specific pharmacist review are essential before dispensing.

Contraindications

Liothyronine 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). Hypersensitivity to liothyronine sodium or to a tablet excipient is also a contraindication for the affected product [41].

Caution is required in: cardiovascular disease (ischemic heart disease, arrhythmia, untreated hypertension); elderly patients (start at 5 mcg daily); diabetes mellitus (T3 may increase insulin or oral hypoglycemic requirements); diabetes insipidus; and patients receiving anticoagulants (thyroid hormone potentiates anticoagulant effect via increased catabolism of vitamin K-dependent clotting factors).

Thyroid hormone is not contraindicated in pregnancy when used for replacement therapy for documented hypothyroidism; untreated maternal hypothyroidism harms fetal development [3]. Pregnancy typically requires an increased L-T4 dose, with TSH monitored each trimester. Thyroid hormones are not appropriate for non-thyroid indications during pregnancy.

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 liothyronine in anticoagulated patients [19].

Insulin and oral hypoglycemic agents: thyroid hormone replacement may increase insulin or oral hypoglycemic requirements as hypothyroidism resolves [19]. Reassess glucose control during titration.

Sympathomimetic amines: combination of thyroid hormone with sympathomimetic amines (e.g., for obesity) is contraindicated due to cardiovascular risk [41] [19].

Bile acid sequestrants, calcium and iron supplements, proton pump inhibitors, and oral estrogen: these and other agents affect absorption or transport of thyroid hormones and require dose-time separation or dose adjustment [19]. The interaction profile is similar to that of L-T4 and is detailed in the Cytomel and Synthroid labels [41].

Tricyclic antidepressants and SSRIs in the depression-augmentation context: T3 augmentation of TCAs [17] and of SSRIs (Cooper-Kazaz 2007) is the intended interaction; clinicians should monitor for serotonergic and adrenergic symptoms during initiation [19].

Adverse events

Adverse events with liothyronine 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. The supraphysiologic post-dose peak after immediate-release tablets [7] can produce transient symptoms even at appropriate total daily dose, particularly with once-daily administration.

Cardiovascular: atrial fibrillation in older adults is the most clinically important arrhythmia signal associated with thyroid hormone excess [3536]. The Flynn 2010 JCEM analysis [34] linked suppressed TSH on long-term thyroxine therapy to cardiovascular morbidity and fracture risk. Angina precipitation is a concern in patients with established ischemic heart disease starting therapy; the recommended starting dose in such patients is 5 mcg daily with slow titration.

Bone: chronic over-replacement is associated with reduced bone mineral density and increased fracture risk, particularly in postmenopausal women and older men [34]. This is a pharmacologic effect of suppressed TSH and elevated FT3 on osteoclast activity.

Allergic / hypersensitivity reactions to liothyronine itself are rare; reactions to excipients in commercial tablets (lactose, modified food starch, calcium sulfate, gelatin) are more common and are one of the documented indications for compounded allergen-free preparations [41].

Adverse events with compounded sustained-release liothyronine specifically are not characterized in published controlled-trial datasets. Theoretical concerns include unpredictable release profile if the formulation has not been adequately characterized, leading either to peak-trough excursions resembling immediate-release Cytomel or to under-delivery. Pharmacy-specific stability and release data are the principal mitigation.

Monitoring Compounded T3 (Liothyronine) Therapy

Baseline assessment should document the etiology of hypothyroidism (autoimmune, post-ablative, post-surgical, central), age, cardiovascular status, current thyroid medications, and the reason combination therapy or a compounded preparation is being considered [jonklaas2014_ata]. Baseline labs include TSH, free T4, free T3, and where relevant lipid panel and HbA1c.

On therapy: TSH is the primary monitoring parameter for L-T4 monotherapy. When combination T4+T3 therapy is used, TSH alone is no longer fully reliable because the post-dose T3 peak from immediate-release liothyronine transiently suppresses TSH [celi2011]. 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 [jonklaas2021_consensus] notes the limitations of TSH-only monitoring under combination regimens.

Reassessment intervals: 6, 8 weeks after any dose change; 6, 12 months once stable [jonklaas2014_ata]. For combination-therapy trials, a pre-specified 3, 6 month review with symptom and laboratory endpoints determines whether the trial is continued.

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 [flynn2010]. 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 of therapy. DEXA every 1, 2 years is reasonable in postmenopausal women and older men with chronically suppressed TSH on combination or supraphysiologic therapy [celi2011].

Compounded T3 (Liothyronine) in Special Populations

Compounded T3 (Liothyronine) Evidence Quality

Evidence supporting the FDA-approved manufactured products (Cytomel, generic liothyronine, Triostat) is strong: decades of clinical use, labeled indications for replacement / supplemental thyroid hormone, TSH suppression in thyroid cancer, and myxedema coma [fda_label_cytomel]. The pharmacology of T3,

receptor binding, deiodinase-mediated production, half-life, peak-trough behavior, is exhaustively characterized [celi2011, bianco_dio2_review, hoermann2015].

Evidence for combination T4+T3 therapy in routine primary hypothyroidism is mixed. The Bunevicius 1999 NEJM signal [bunevicius1999] has not been consistently replicated. Walsh 2003 [walsh2003], Clyde 2003 [clyde2003], Appelhof 2005 [appelhof2005], Nygaard 2009 [nygaard2009], and Shakir 2021 [shakir2021] are predominantly null on primary endpoints. The Grozinsky-Glasberg 2006 meta-analysis [grozinsky2006] and Ma 2009 meta-analysis [ma_combination_meta] conclude no consistent benefit. The 2014 ATA guideline [jonklaas2014_ata] reflects this: L-T4 monotherapy is first-line. The 2012 ETA [wiersinga2012_eta] and 2021 joint ATA/ETA/BTA consensus [jonklaas2021_consensus] permit individualized trials of combination therapy in patients with persistent symptoms despite adequate monotherapy.

Evidence for a responder phenotype identified by DIO2 polymorphism [panicker2009_dio2] [panicker2009_dio2] is biologically plausible and the strongest available signal of patient selection, but the finding has not been prospectively replicated and the Appelhof 2005 dataset did not support it [appelhof2005_dio2]. Population genotyping is not currently recommended.

Evidence for compounded sustained-release liothyronine specifically is limited. The mechanistic rationale from Celi 2011 [celi2011] is robust, immediate-release liothyronine produces non-physiologic peaks, and a sustained-release approach can flatten them. The translation to formal phase-3-equivalent clinical efficacy data for compounded SR liothyronine does not exist. Compounded use is therefore an individualized application of the broader combination-therapy evidence base, justified case-by-case by the prescribing clinician with documented patient-specific clinical rationale.

Evidence for T3 augmentation in major depressive disorder is more robust than for combination hypothyroidism therapy: Joffe 1993 RCT [joffe1993], Aronson 1996 meta-analysis [aronson1996], Cooper-Kazaz 2007 RCT [cooper_kazaz2007], and the STAR*D level-3 result [nierenberg2006_stard] together support T3 as one of several reasonable augmentation strategies after partial or non-response to standard antidepressant monotherapy. Durability of benefit is limited.

Major Compounded T3 (Liothyronine) Clinical Studies

Study	Design	Participants	Duration	Finding
Bunevicius et al. (1999, NEJM)	Randomized double-blind crossover trial substituting 12.5 mcg of T3 for 50 mcg of T4 in standard L-T4 regimens	33	5 weeks per arm	Improved mood and neuropsychological function on partial T4-to-T3 substitution compared with L-T4 monotherapy, generated the modern combination-therapy debate [bunevicius1999]

Study	Design	Participants	Duration	Finding
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 [bunevicius2002]
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 [walsh2003]
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 [clyde2003]
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 [appelhof2005]
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 [appelhof2005_dio2]
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 [grozinsky2006].
		59	12 weeks per arm	Combination therapy was preferred by 49% of patients vs 15%

Study	Design	Participants	Duration	Finding
Nygaard et al. (2009, Eur J Endocrinol)	Randomized double-blind crossover, T4 vs T4+T3			preferring monotherapy; modest improvement in some quality-of-life domains [nygaard2009]
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 [panicker2009_dio2]
Ma et al. (2009, Nucl Med Commun)	Meta-analysis of randomized trials of T4 monotherapy versus T4+T3 combination	—	—	No statistically significant difference in symptom scores, lipid profile, body weight, or quality of life between regimens [ma_combination_meta]
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 [celi2011]
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 compared with euthyroid controls, evidence that L-T4 monotherapy does not fully normalize peripheral T3 in patients without a thyroid gland [gullo2011]
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, but 48.6% of patients preferred DTE; the DTE arm produced modest weight loss [hoang2013]

Study	Design	Participants	Duration	Finding
Shakir et al. (2021, JCEM)	Randomized double-blind three-arm crossover: L-T4, desiccated thyroid extract, and L-T4 + L-T3	75	Three 22-week arms	No clinically meaningful between-arm differences in symptom or quality-of-life measures; patient preferences distributed across the three regimens [shakir2021]
Bunevicius 1999 (NEJM), landmark crossover (also listed above as primary study)	See above	—	—	See above [bunevicius1999]
Klemperer et al. (1995, NEJM)	Randomized double-blind placebo-controlled trial of low-dose IV T3 during coronary-artery bypass surgery	142	Surgery and 24-hour post-bypass period	Improved cardiac index and reduced inotrope requirement post-bypass; established a short-term cardiac role for IV T3 in this context [klemperer1995]
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, established T3 augmentation as a viable strategy [joffe1993]
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 [aronson1996]
Cooper-Kazaz et al. (2007, Arch Gen Psychiatry)	Randomized double-blind placebo-controlled trial of combined sertraline + T3 from treatment initiation vs	124	8 weeks	Combined sertraline + T3 superior to sertraline alone on depression rating scales and response/ remission rates [cooper_kazaz2007]

Study	Design	Participants	Duration	Finding
	sertraline alone in major depression			
Nierenberg et al. (2006, Am J Psychiatry), STAR*D level 3	Randomized open-label comparison of T3 augmentation vs lithium augmentation in patients with 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 [nierenberg2006_stard]
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 [flynn2010]
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 [escobar_morreale_rat]
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 [ito_atrophic]
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 [ito2019]
Sawin et al. (2002, Thyroid; Surks 2004 JAMA	Review / cohort analyses of atrial fibrillation in	—	—	Suppressed TSH is associated with atrial fibrillation in older adults, relevant to avoiding over-

Study	Design	Participants	Duration	Finding
consensus review)	subclinical hyperthyroidism			replacement on chronic T3 therapy [sawin_afib; surks2004]
Jonklaas et al. (2014, Thyroid), ATA 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 with persistent symptoms [jonklaas2014_ata]
Wiersinga et al. (2012, Eur Thyroid J), ETA 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 [wiersinga2012_eta]
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; population-level DIO2 genotyping not recommended [jonklaas2021_consensus]
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 sustained-release liothyronine [ettleson_bianco]
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 biochemically detectable peripheral T3 deficit and

Study	Design	Participants	Duration	Finding
				persistent symptoms [mcaninch2015]
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 [hennessey2015]
Hennessey (2017, Endocrine)	Historical review	—	—	Documents the emergence of levothyroxine as the standard thyroid hormone replacement therapy [hennessey2017_emergence]
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 [hoermann2015]
Biondi & Wartofsky (2012, JCEM)	Review of combination T4+T3 treatment in hypothyroidism	—	—	Frames the case for personalized replacement and identifies athyreotic and DIO2-polymorphism subsets as candidates for combination therapy [biondi2012]
Dayan & Panicker (2018, Thyroid Research)	Practical review	—	—	Provides guidance on the practical implementation of combination T4+T3 therapy in patients with persistent symptoms [dayan_panicker]
Perros et al. (2021, Eur J Endocrinol)	Risk-of-death-based analysis of therapeutic targets for L-T4-treated primary hypothyroidism	—	—	Informs the range of TSH values associated with optimal long-term outcomes in L-T4-treated hypothyroidism, informs combination-therapy monitoring [perros2021]
	Review of subclinical thyroid dysfunction	—	—	Catalogs cardiovascular and bone consequences of chronically

Study	Design	Participants	Duration	Finding
Biondi & Cooper (2008, Endocr Rev)				suppressed TSH, frames the safety boundary of T3-containing regimens [biondi_cooper2008]
Biondi & Klein (2004, Endocrine)	Review	—	—	Reviews hypothyroidism and hyperthyroidism as cardiovascular-risk modifiers [biondi_klein2004]

Compounded T3 (Liothyronine) Pharmacokinetics & Pharmacodynamics

Pharmacokinetics

Liothyronine sodium is rapidly absorbed after oral administration of immediate-release Cytomel; bioavailability approaches 95% in fasting adults [fda_label_cytomel]. Tmax is 2, 4 hours, and post-dose peak serum T3 is approximately 30, 40% above baseline at replacement doses [celi2011]. Terminal half-life is approximately 24 hours in euthyroid adults but is shorter in hyperthyroidism and longer in hypothyroidism. Protein binding is high (~99.7%) to thyroxine-binding globulin (TBG), transthyretin (TTR), and albumin, with the small free fraction biologically active. T3 is metabolized predominantly by inner-ring deiodination (DIO3) and by glucuronidation and sulfation; clearance is hepatic with renal excretion of conjugated metabolites a secondary pathway.

Compounded sustained-release liothyronine capsules are formulated with controlled-release excipients designed to extend the absorption window across 8, 24 hours. The release profile depends on the specific formulation (matrix or coated-bead; excipient identity and ratio) and is documented per the pharmacy's product-specific data. Compounded SR preparations are not bioequivalent to Cytomel and the PK characteristics published for Cytomel should not be assumed to translate without local stability and release data [fda_label_cytomel].

Drug-drug PK interactions are similar to L-T4: bile acid sequestrants, calcium and iron supplements, and proton pump inhibitors reduce thyroid hormone absorption; oral estrogen elevates TBG and increases the required dose; phenytoin and rifampin accelerate hepatic clearance and may increase requirements [fda_label_cytomel].

Pharmacodynamics

Pharmacodynamic effects of T3 are mediated by nuclear thyroid hormone receptor (TRα, TRβ) occupancy and downstream regulation of thyroid-hormone-response-element-containing target genes. Net effects include 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 [celi2011].

The principal measured pharmacodynamic endpoints in clinical practice are TSH (the integrated pituitary feedback signal), free T4, and free T3 (the latter ideally drawn at trough relative to the most recent T3 dose). Patient-reported symptoms, energy, mood, cognitive function, cold intolerance, weight, are weighted alongside the laboratory metrics in individualized titration. In combination therapy regimens TSH-only monitoring is incomplete because the post-dose T3 peak from immediate-release liothyronine transiently suppresses TSH; supplementing with FT3 measurement is standard [jonklaas2021_consensus, hoermann2015] [fda_label_cytomel; celi2011].

↓↑ Comparing Compounded T3 (Liothyronine) Formulations

The manufactured immediate-release Cytomel and generic liothyronine tablets at 5, 25, and 50 mcg are the reference products for outpatient oral T3 [fda_label_cytomel]. They are FDA-approved, widely available, low-cost, and supported by decades of clinical use. Their principal limitation is the supraphysiologic post-dose serum T3 peak that follows once-daily administration [celi2011].

Compounded sustained-release liothyronine capsules attenuate the post-dose peak by extending the absorption window. They are not bioequivalent to Cytomel and are individualized to the patient's prescription and the pharmacy's product [fda_label_cytomel]. Documented stability and release-profile data are necessary.

Compounded custom-strength immediate-release capsules deliver doses below or between the commercial 5/25/50 mcg increments. Their PK behavior is expected to parallel Cytomel (immediate-release absorption pattern) at the prescribed lower dose; the principal advantage is the gravimetrically verified accurate dose, not a PK modification [fda_label_cytomel].

Allergen-free or excipient-substituted preparations have the same PK behavior as standard Cytomel at matched dose, differing only in the excipient profile [fda_label_cytomel].

Compounded oral suspensions allow weight-based pediatric dosing and easier administration in dysphagic adults. Stability is product-specific [hennessey2015].

🌡 Compounded T3 (Liothyronine) Storage and Handling

Manufactured Cytomel and generic liothyronine sodium tablets are stored at 20, 25°C (68, 77°F) with excursions permitted to 15, 30°C, protected from light and moisture, per labeling [fda_label_cytomel] [usp_795]. Compounded liothyronine capsules and suspensions are stored per the pharmacy's product-specific stability data and beyond-use date assignment under USP <795>; refrigeration may be required for certain suspension formulations.

Liothyronine is not a cold-chain product in the same sense as biologics or some peptides; standard controlled room temperature storage is sufficient for the manufactured tablets and most compounded capsules [usp_795].

Compounded T3 (Liothyronine) Compounding & Operations

503A compounding

Compounded liothyronine is prepared under 503A on patient-specific prescriptions in state-licensed compounding pharmacies. RonanRx prepares oral capsules and suspensions per USP General Chapter <795> (Pharmaceutical Compounding, Nonsterile Preparations), with documented active ingredient sourcing 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 [fda503a; usp_795].

Sustained-release liothyronine capsules 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 [jonklaas2021_consensus] acknowledges the absence of a manufactured sustained-release liothyronine product in the United States and recognizes compounded SR preparations as a clinically reasonable approach for combination therapy [usp_795].

Beyond-use dating, ingredient identity verification, and stability assessment follow USP <795> [fda503a]. Each compounded batch is documented per state board of pharmacy retention rules.

Pharmacist review

Each prescription for compounded liothyronine undergoes pharmacist review prior to dispensing. The review confirms: a documented patient-specific clinical reason that the manufactured Cytomel or generic liothyronine tablet is not appropriate (sustained-release pharmacokinetic profile, sub-5-mcg titration step, excipient sensitivity, or pediatric/dysphagic suspension need); absence of contraindications (uncorrected adrenal insufficiency, untreated thyrotoxicosis); appropriate concomitant medication review (anticoagulants, insulin and oral hypoglycemics, oral contraception or estrogen therapy, sympathomimetic agents); and a prescribed regimen consistent with published clinical-trial regimens or current ATA/ETA/BTA consensus guidance [jonklaas2014_ata, jonklaas2021_consensus] [fda_label_cytomel].

RonanRx does not fill prescriptions that read as routine substitution of compounded immediate-release liothyronine for Cytomel without documented clinical rationale, consistent with FDA guidance on compounded copies of commercially available drugs [fda_essentially_a_copy] [fda_label_cytomel]. Compounded sustained-release liothyronine, custom sub-5-mcg strengths, allergen-free preparations, and pediatric suspensions are the well-defined 503A roles for compounded T3 that meet the patient-specific clinical need threshold.

Quality and traceability

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

Cold chain

Liothyronine tablets and most compounded liothyronine capsules are stable at controlled room temperature and do not require cold-chain transport [fda_label_cytomel]. Certain compounded oral suspensions may require refrigerated storage per the pharmacy's product-specific stability data; the dispensing label and patient counseling will specify storage requirements when refrigeration is needed [usp_795].

Frequently Asked Questions About Compounded T3 (Liothyronine)

What is the difference between T4 and T3, and why does it matter?

T4 (levothyroxine, Synthroid) is the storage hormone that the thyroid gland makes in the largest amount; T3 is the active hormone that actually works inside cells [bianco_dio2_review]. The body converts T4 to T3 in tissues like the liver, brain, and muscle. Standard hypothyroidism treatment uses T4 alone because the conversion is usually adequate [jonklaas2014_ata]. Some patients still feel unwell on T4 alone, and adding a small amount of T3 is one option clinicians consider.

Is compounded T3 the same as Cytomel?

No. Cytomel and generic liothyronine tablets are FDA-approved manufactured products in 5, 25, and 50 mcg strengths [fda_label_cytomel]. Compounded liothyronine is pharmacy-prepared for a specific patient, typically as a sustained-release capsule, a custom strength below or between the commercial sizes, an allergen-free version, or an oral suspension. Compounded preparations are not FDA-approved and are not bioequivalent to Cytomel [fda503a].

Why would my doctor prescribe sustained-release T3?

Immediate-release Cytomel produces a peak in serum T3 about 2, 4 hours after dosing that is roughly 30, 40% above baseline. A healthy gland does not produce that peak. Sustained-release compounded capsules are designed to spread the T3 dose across the day to produce steadier levels. The 2021 ATA/ETA/BTA consensus document acknowledges the pharmacokinetic limitations of immediate-release liothyronine and

recognizes sustained-release preparations as a clinically reasonable approach for combination therapy [celi2011; jonklaas2021_consensus].

Does adding T3 to T4 actually help with hypothyroidism symptoms?

It depends. The Bunevicius 1999 NEJM trial reported mood and cognitive benefit on partial T4-to-T3 substitution, but multiple larger trials (Walsh 2003, Clyde 2003, Appelhof 2005, Nygaard 2009, Shakir 2021) did not show consistent improvement in unselected patients [bunevicius1999]. Meta-analyses (Grozinsky-Glasberg 2006, Ma 2009) found no overall benefit on quality of life [walsh2003]. Patient preference often favors combination therapy in crossover trials. The 2021 joint ATA/ETA/BTA consensus document supports a trial of combination therapy in selected patients with persistent symptoms despite adequate L-T4 monotherapy [appelhof2005; grozinsky2006; jonklaas2021_consensus].

What is the DIO2 polymorphism and should I be tested?

DIO2 is the gene for the type 2 deiodinase, the enzyme that converts T4 to T3 inside the brain and several other tissues. The Thr92Ala (rs225014) polymorphism is a common variant. Panicker 2009 reported that homozygotes for the Ala allele had lower baseline well-being on T4 monotherapy and greater symptomatic benefit from combination therapy [panicker2009_dio2]. This finding has not been prospectively replicated in a powered trial, and the 2014 ATA guideline, 2012 ETA guideline, and 2021 joint consensus do not recommend population genotyping [jonklaas2021_consensus].

When is a compounded T3 preparation appropriate?

Per FDA guidance, a compounded version of an FDA-approved drug is appropriate when the prescriber documents a patient-specific clinical need the manufactured product cannot meet [fda_essentially_a_copy]. For T3, the typical documented needs are: sustained-release pharmacokinetics, custom strengths below 5 mcg or between commercial increments, excipient sensitivity (Cytomel contains lactose, modified food starch, calcium sulfate), and oral suspension for pediatric or dysphagic patients [fda503a]. Cost or preference alone does not qualify.

Can T3 be used for depression?

T3 has been studied as an augmentation strategy for major depressive disorder partially or unresponsive to standard antidepressants [nierenberg2006_stard]. The Joffe 1993, Aronson 1996 meta-analysis, Cooper-Kazaz 2007 sertraline-augmentation trial, and the STAR*D level-3 result all support T3 as one of several reasonable augmentation options [joffe1993; aronson1996; cooper_kazaz2007]. This is an off-label use; durability of benefit is limited and clinical decisions are individualized.

Is T3 safe for the heart?

Liothyronine at appropriate replacement doses is generally well tolerated. The principal cardiac concerns are atrial fibrillation in older adults with chronically suppressed TSH and angina precipitation in patients

with established ischemic heart disease starting therapy [sawin_afib]. Older patients and those with cardiac disease should start at 5 mcg daily with slow titration [surks2004]. The Flynn 2010 JCEM cohort linked suppressed TSH on long-term thyroxine therapy to cardiovascular morbidity and fractures, so combination regimens should not produce a chronically suppressed TSH unless TSH suppression is the explicit goal [flynn2010].

Can T3 be used for weight loss?

No. The Cytomel label specifically warns that thyroid hormones are not appropriate for the treatment of obesity, alone or combined with other drugs, and that such use may be hazardous. The historical 'rainbow diet pill' combination of thyroid hormone with sympathomimetic amines is contraindicated due to cardiovascular harm. Liothyronine is on the WADA prohibited list in some sport contexts [fda_label_cytomel; wada_prohibited].

Does RonanRx sell compounded T3 directly to patients?

No. Compounded liothyronine requires a patient-specific prescription from a licensed doctor for an identified patient with a documented clinical reason the manufactured Cytomel is not appropriate, plus pharmacist review before dispensing [fda_essentially_a_copy]. RonanRx is not a direct-to-consumer storefront [fda503a].

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How to Access Compounded T3 (Liothyronine)

Compounded Compounded T3 (Liothyronine) 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 (Liothyronine), sign up so we can prepare and ship your medication. The signup wizard collects intake and connects you to the prescribing workflow.

ronanrx.com/patients

PATIENT WITHOUT A DOCTOR

Find a partner clinic

RonanRx prescribes through partner clinics — we don't initiate prescriptions on this site. Read how the referral process works and how to find a partner clinic in your state.

ronanrx.com/find-clinic

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 (40)

Alpha-Lipoic Acid (ALA) — Antioxidant & mitochondrial
Coenzyme Q10 (CoQ10) — Antioxidant & mitochondrial
Glutathione — 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
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)