CLINICAL MONOGRAPH · THYROID

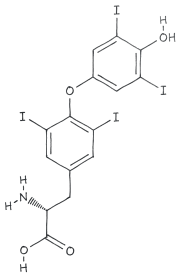
Compounded T4 (Levothyroxine)

Levothyroxine compounded for excipient sensitivity or custom dosing

Levothyroxine, often called T4, is a synthetic copy of the main hormone your thyroid gland makes. It is prescribed to people whose thyroid does not make enough hormone, a condition called hypothyroidism, and it is one of the most commonly prescribed medications in the United States [jonklaas2014ata; garber2012aace] [selva2002]. The brand-name versions include Synthroid, Levoxyl, Unithroid, Tirosint (a gel capsule), and Tirosint-SOL (a liquid). All of them are FDA-approved.

Most people do well on a standard manufactured levothyroxine tablet. RonanRx compounds levothyroxine only when a manufactured product cannot meet a patient's specific need [fda_label_synthroid]. The most common reasons are sensitivity to an ingredient in the commercial tablet, like lactose, gluten, dyes, soy, or specific binders, a need for a strength smaller than the smallest commercial pill (25 mcg) or an in-between strength (like 12.5 or 18.75 mcg) for fine-tuning, or a need for a liquid preparation for an infant, child, or adult who cannot swallow a tablet.

Levothyroxine is taken by mouth, on an empty stomach, ideally 30, 60 minutes before breakfast, with water only. The dose is titrated based on a blood test called TSH, with the goal of getting TSH into the normal range. The hormone has a long half-life of about a week, so missed doses are not immediately dangerous, but consistency matters because it is a narrow-therapeutic-index drug, small dose differences can produce symptoms of over- or under-treatment [fda_label_synthroid; fda_label_tirosint; salerno2002].



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

Levothyroxine sodium is first-line treatment for overt primary hypothyroidism, central hypothyroidism, and post-thyroidectomy hormone replacement, with on-label use for TSH suppression in differentiated thyroid cancer per the ATA 2015 management guidelines [haugen2015ata] and the prior ATA 2009 guideline by Cooper and colleagues [cooper2009ata] [fda_label_synthroid]. The ATA 2014 hypothyroidism treatment guidelines [jonklaas2014ata] and the AACE/ATA 2012 cosponsored guidelines [garber2012aace] recommend levothyroxine monotherapy as the standard of care; the ETA 2012 guidelines [wiersinga2012eta] and the McAninch, Bianco 2015 mechanistic review [mcaninch_bianco2015] address combination L-T4/L-T3 only for selected patients who remain symptomatic on monotherapy, with the Akirov 2019 IPD-meta of patient preference [akirov2019] showing modest but reproducible preference for combination in some series. Subclinical hypothyroidism (TSH 4.5, 10 mIU/L with normal free T4) is a gray area: the TRUST trial in adults ≥65 [stott2017trust] found no symptomatic benefit from levothyroxine treatment in mild subclinical hypothyroidism, the Cochrane review by Villar [villar2007cochrane] previously reached a similar null, and the Roos 2005 RCT [roos2005] established that a fixed full-replacement starting dose is non-inferior to titrated low-dose initiation in primary hypothyroidism. The ETA 2013 subclinical hypothyroidism guideline [pearce2013eta] frames treatment decisions by age, TSH magnitude, symptoms, and cardiovascular risk; cardiovascular evidence is anchored by Razvi 2008 age-stratified meta [razvi2008], Razvi 2012 cohort of LT4 treatment and CV events [razvi2012], the Rodondi 2010 JAMA individual-participant-data meta [rodondi2010], the Cappola 2006 JAMA elderly cohort [cappola2006], and the Selmer 2014 Danish nationwide cohort [selmer2014].

Replacement dose is approximately 1.6 mcg/kg/day in adults with overt hypothyroidism [devdhar2011], lower in elderly and those with cardiac disease (start 12.5, 25 mcg) and substantially higher in pregnancy (typically a 25, 50% dose increase confirmed by Alexander 2017 ATA pregnancy guidelines [alexander2017ata] and the Negro 2010 universal screening trial [negro2010]; the Alexander 2004 NEJM time-course study [alexander2004] originally quantified the early-pregnancy dose increase). Pediatric dosing is weight-based and age-stratified per Selva [selva2002], Salerno [salerno2002], LaFranchi's 2011 JCEM update [lafranchi2011], and the Léger 2014 European Society for Paediatric Endocrinology consensus [leger2014], with substantially higher starting doses in congenital hypothyroidism (10, 15 mcg/kg/day). Levothyroxine was designated by FDA as a narrow therapeutic index drug in 2017; small absorption and formulation differences can produce clinically meaningful TSH changes, and Hennessey 2022 reviewed the implications for generic-to-generic switching [hennessey2022switching] [fda_label_tirosint]. Vita and colleagues [vita2014, yue2012] demonstrated that liquid and soft-gel formulations (Tirosint, Tirosint-SOL) produce less variable absorption than tablet formulations, with the Pabla 2009 pH-dissolution comparison [pabla2009] providing the in vitro mechanism, particularly in patients with achlorhydria, atrophic gastritis, Helicobacter pylori infection, celiac disease, or PPI use [centanni2006, liwanpo2009, lahner_virili2014]; coffee taken within 60 minutes of a tablet dose impairs absorption [benvenga_coffee2008] and the Pirola 2018 study [pirola_breakfast2018] demonstrated equivalent TSH control taking liquid LT4 at breakfast versus 30 minutes before.

Compounded levothyroxine occupies a narrow legitimate 503A niche given the breadth of the FDA-approved market, generic levothyroxine and Tirosint-SOL together cover most dosing and absorption needs. RonanRx compounds levothyroxine when the prescriber documents one of: (1) sensitivity to an excipient in available commercial products (acacia, lactose, talc, FD&C dyes, gluten, soy lecithin), (2) a custom strength below 25 mcg (the smallest Synthroid increment) or between commercial increments, typical examples include 12.5, 18.75, 37.5 mcg used for fine titration in patients with narrow tolerance windows, or (3) a pediatric or geriatric patient requiring a liquid suspension at a concentration not available as Tirosint-SOL [fda_label_tirosint_sol]. Compounded preparations are not bioequivalent

to manufactured tablets; patients switching between manufactured and compounded levothyroxine require TSH reassessment 6, 8 weeks after the switch per FDA narrow therapeutic index designation, consistent with the Andersen 2002 demonstration [andersen2002] that within-person variation in serum T4 and TSH is much narrower than the population reference range, small dose changes produce out-of-range TSH for an individual who was previously in-range [fda_label_synthroid].

Why Personalized Compounded T4 (Levothyroxine)

Levothyroxine is the FDA's textbook narrow-therapeutic-index drug. The manufactured tablet strengths (25, 50, 75, 88, 100, 112, 125, 137 mcg and up) were chosen to cover the population, not to fit one thyroid. They were also formulated with a fixed excipient deck: lactose, FD&C dyes, talc, sometimes gluten or soy lecithin. The dose that puts your TSH in range may sit between two commercial steps. The binder that puts a rash on your forearm is locked into the tablet you were handed.

That is where compounding earns its place. The molecule is the same levothyroxine sodium the FDA reviewed in 1955. A 503A pharmacy can hit a 12.5, 18.75, or 37.5 mcg strength that no manufacturer makes, build the capsule without the excipient your chart says you react to, or prepare a liquid at a concentration Tirosint-SOL does not stock for an infant or an adult who cannot swallow a tablet. None of that is substitution for Synthroid. It is the part of the dose space the manufactured market chose not to fill.

This is the older arrangement that predates mass-manufactured tablets: a prescriber who knows the patient, a pharmacist who prepares the dose, a label with the patient's name on it. Modern state-board inspection and FDA 503A oversight keep it honest.

Quick Facts About Compounded T4 (Levothyroxine)

Category: Endogenous thyroid hormone (prohormone); synthetic levothyroxine sodium

Active ingredient: Levothyroxine sodium, the synthetic sodium salt of the L-isomer of thyroxine (T4), bioidentical to endogenous T4

FDA-approved branded products: Synthroid (tablet, AbbVie), Levoxyl (tablet, Pfizer), Unithroid (tablet, Lannett), Tirosint (liquid-filled gelatin capsule, IBSA), Tirosint-SOL (oral solution, IBSA), Euthyrox (tablet, Provell), Levo-T (tablet), generic levothyroxine sodium tablets

Routes studied in humans: Oral (tablet, soft-gel capsule, liquid solution) is standard; intravenous levothyroxine is reserved for myxedema coma and inability to take oral

Evidence posture: FDA-approved manufactured products are well-studied; landmark guidelines and trials include the ATA 2014 hypothyroidism guidelines (Jonklaas), the AACE/ATA 2012 guidelines (Garber), the ETA 2012/2013 guidelines (Wiersinga, Pearce), and the TRUST trial (Stott 2017 NEJM) in older adults with subclinical hypothyroidism

FDA-approval status: Multiple FDA-approved manufactured levothyroxine products are available; levothyroxine was designated a narrow therapeutic index drug by FDA in 2017. Compounded levothyroxine is not FDA-approved but addresses patient-specific clinical needs that the manufactured market does not meet, excipient sensitivity, custom strengths below or between commercial steps, and pediatric liquid preparations.

Compounded under: 503A, patient-specific prescription only; not a controlled substance

Compounded role: Distinct from 'essentially-a-copy' substitution: patient-specific compounding addresses excipient sensitivity (lactose, dyes, gluten, soy in manufactured tablets), custom strengths below the 25 mcg Synthroid minimum or between commercial increments (12.5, 18.75, 37.5 mcg), and pediatric liquid preparations at concentrations not available commercially.

Schedule: Not a controlled substance

Pregnancy category: Category A, treatment of overt hypothyroidism is required during pregnancy; dose typically increases by 25, 50% on confirmation of pregnancy. Levothyroxine crosses the placenta minimally at physiologic doses.

> **SPECIALS: PATIENT-SPECIFIC PRESCRIPTION ONLY**
>
> Compounded T4 (Levothyroxine) 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 T4 (Levothyroxine)?

Levothyroxine sodium is the synthetic sodium salt of the L-isomer of thyroxine (T4), chemically identical to the principal hormone produced by the thyroid gland. The thyroid gland synthesizes T4 as a prohormone by iodinating tyrosine residues on thyroglobulin under thyroid-stimulating hormone (TSH) control; T4 has limited intrinsic activity at the thyroid hormone receptor and acts primarily as a circulating reservoir that is deiodinated peripherally to the active hormone T3 [jonklaas2014ata].

Levothyroxine was first synthesized in 1927 by Harington and Barger and entered clinical use in the 1950s, gradually replacing desiccated thyroid extract as the standard therapy for hypothyroidism through the 1960s and 1970s [jonklaas2014ata]. Synthroid was FDA-approved in 1955 and remains the dominant branded product; multiple generic and branded alternatives became available across the 1980s through 2010s. Tirosint (liquid-filled gelatin capsule, 2009) and Tirosint-SOL (oral solution, 2016) were specifically developed to address absorption variability seen with conventional tablets [vita2014, yue2012].

The drug is dispensed orally as tablets, soft-gel capsules, or oral solution [fda_label_synthroid; fda_label_tirosint; fda_label_tirosint_sol]. Tablet strengths from FDA-approved manufacturers include 25, 50, 75, 88, 100, 112, 125, 137, 150, 175, 200, and 300 mcg, a narrow-increment range that supports the narrow-therapeutic-index dose-titration regimen. Tirosint and Tirosint-SOL are available at additional intermediate strengths. Compounded preparations supplement this with custom strengths below 25 mcg or between commercial increments, and with allergen-free formulations and pediatric-friendly liquid preparations.

How Compounded T4 (Levothyroxine) Works

Levothyroxine is a prohormone. After oral absorption (predominantly in jejunum and upper ileum), circulating T4 is largely (>99%) bound to thyroxine-binding globulin (TBG), transthyretin, and albumin; the free fraction (~0.03%) diffuses into target cells. Within target tissues, T4 is deiodinated by type 1 and type 2 5'-deiodinases to the biologically active T3, which binds nuclear thyroid hormone receptors (TR-alpha and TR-beta) and regulates transcription of thyroid-responsive genes [jonklaas2014ata]. Approximately 80% of circulating T3 is generated from peripheral T4 deiodination rather than from direct thyroidal secretion.

Tissue-level T3 exposure is thus tightly regulated by local deiodinase activity, which differs by tissue and physiologic state. This is the molecular basis for why T4 replacement alone restores euthyroid physiology in the great majority of hypothyroid patients, peripheral conversion provides the active hormone in a tissue-

specific, autoregulated fashion [jonklaas2014ata]. The minority of patients who remain symptomatic on T4 monotherapy is the population for whom the ETA 2012 combination guidelines [wiersinga2012eta] articulate the rationale for a closely-monitored T4/T3 trial.

Levothyroxine has a serum half-life of approximately 7 days in euthyroid adults, supporting once-daily oral dosing with stable steady-state serum concentrations. Steady state after a dose change is reached in approximately 4, 6 weeks, which is the basis for the 6, 8 week TSH check-and-titrate interval used in clinical practice [garber2012aace].

Biological Role of Compounded T4 (Levothyroxine)

Thyroid hormone is a master regulator of basal metabolic rate, thermogenesis, growth, neurodevelopment, and the activity of nearly every tissue. In adults, thyroid hormone modulates cardiac contractility and heart rate, lipid metabolism, gut motility, bone turnover, mood, cognition, and the menstrual cycle. In the fetus and neonate, thyroid hormone is essential for central nervous system maturation; untreated congenital hypothyroidism produces irreversible cognitive impairment, motivating newborn screening programs worldwide and the very-early-treatment dosing strategy validated by Selva [selva2002] and Salerno [salerno2002].

Hypothyroidism prevalence in the general population is approximately 4, 5% overt plus subclinical, with subclinical predominating. The Hollowell NHANES III analysis [hollowell2002nhanes] characterized the U.S. prevalence and reference range distribution. The Tunbridge Whickham survey [tunbridge1977whickham] and the Vanderpump 20-year follow-up [vanderpump1995whickham] established population-level incidence and progression rates of subclinical to overt disease in a UK community cohort, anchoring the modern epidemiology of autoimmune thyroid disease. TSH reference range varies with age, Vadiveloo and colleagues [vadiveloo2013tears] demonstrated rising TSH with age in disease-free Scottish adults, which has subsequent implications for the diagnosis of mild subclinical hypothyroidism in older adults.

Endogenous thyroid hormone is required during pregnancy: maternal T4 is the only source of thyroid hormone for the fetus through approximately 16 weeks gestation when the fetal thyroid becomes functional. Maternal hypothyroidism, overt or subclinical, is associated with adverse obstetric outcomes including miscarriage, preterm delivery, and impaired neurodevelopment, addressed in the Alexander 2017 ATA pregnancy guidelines [alexander2017ata], the Negro 2010 universal screening trial [negro2010], the Korevaar Generation R analysis [korevaar2013], and the Casey 2017 NEJM trial of treatment of subclinical hypothyroidism in pregnancy [casey2017].

Detailed Mechanism of Compounded T4 (Levothyroxine)

Hypothalamic-pituitary-thyroid (HPT) axis. The thyroid hormone system is regulated by a negative-feedback loop: hypothalamic thyrotropin-releasing hormone (TRH) stimulates pituitary thyroid-stimulating hormone (TSH); TSH stimulates thyroidal T4 (and a smaller amount of T3) production; circulating T4 and T3 suppress TRH and TSH. TSH is exponentially related to free T4 across the physiologic range, which is why TSH is the most sensitive single measure of thyroid status in primary hypothyroidism, small changes in free T4 produce large, log-linear TSH changes. Levothyroxine replacement is titrated to TSH in primary hypothyroidism and to free T4 in central (pituitary or hypothalamic) hypothyroidism, where TSH is uninformative [jonklaas2014ata].

Deiodinase biology. Three deiodinase enzymes (D1, D2, D3) interconvert thyroid hormones. D1 (liver, kidney, thyroid) is the major source of circulating T3 from T4. D2 (brain, pituitary, brown adipose, thyroid) is the major source of intracellular T3 in those tissues, including the pituitary, which is why pituitary TSH responds tightly to circulating T4 even in athyreotic patients on T4-only replacement. D3 (placenta, brain, fetal tissues) inactivates T4 to reverse T3 and T3 to T2, protecting tissues from excess thyroid hormone exposure during development. Tissue-specific deiodinase expression is the substrate for the longstanding clinical debate over T4 monotherapy versus T4/T3 combination therapy, addressed in the ETA 2012 guidelines [wiersinga2012eta] and the AACE/ATA 2012 guidelines [garber2012aace].

Thyroid hormone receptors. TR-alpha and TR-beta are nuclear hormone receptors expressed in different patterns across tissues, TR-alpha predominates in heart and skeletal muscle, TR-beta in liver, kidney, and the HPT axis. Ligand-bound TR heterodimerizes with retinoid X receptor on thyroid response elements in target-gene promoters and recruits coactivator or corepressor complexes depending on ligand state. Nongenomic effects of T3 on plasma membrane and mitochondrial targets account for some acute thyroid hormone effects on cardiac function and metabolism.

Absorption pharmacology. Levothyroxine absorption from a tablet requires gastric acid to dissolve the tablet matrix and dissociate levothyroxine from sodium. Conditions reducing gastric acid, atrophic gastritis, autoimmune gastritis, Helicobacter pylori infection, prolonged proton pump inhibitor or H2-blocker use, prior gastric bypass, reduce tablet bioavailability and necessitate dose escalation [centanni2006]. Liquid and soft-gel formulations (Tirosint, Tirosint-SOL) bypass this absorption step and produce more reproducible serum levels in patients with malabsorption [vita2014, yue2012]. Other absorption-interfering products include calcium carbonate, ferrous sulfate, aluminum-containing antacids, bile-acid sequestrants, sucralfate, sevelamer, and high-fiber meals, separation of dosing by 4 hours is standard advice. Coffee taken within 60 minutes of levothyroxine reduces absorption of conventional tablets.

Narrow therapeutic index biology. FDA designated levothyroxine a narrow therapeutic index (NTI) drug in 2017 because the therapeutic range and the toxic range overlap closely: small dose changes (12.5 mcg in adults, less in elderly and small patients) produce clinically meaningful TSH changes and over-replacement

is associated with atrial fibrillation, accelerated bone loss, and adverse cardiovascular outcomes. The NTI designation tightened bioequivalence requirements for generic substitution to a 90, 110% range (versus the standard 80, 125%) and underpinned ATA, AACE, and Endocrine Society recommendations that patients remain on the same manufacturer's product through a refill cycle and undergo TSH recheck after any switch.

Compounded T4 (Levothyroxine) Research History

Thyroxine was isolated by Edward Calvin Kendall in 1914 from desiccated thyroid extract and structurally identified as the 3,5,3',5'-tetraiodothyronine in 1926; Harington and Barger synthesized it in 1927. Through the first half of the 20th century, desiccated thyroid extract from porcine or bovine sources was the dominant treatment for myxedema and was associated with the variable potency that motivated the eventual transition to synthetic levothyroxine. Synthroid was FDA-approved in 1955; through the 1970s and 1980s, levothyroxine monotherapy displaced desiccated extract as standard of care, formalized in the AACE/ATA guidelines of the 2000s and 2010s [garber2012aace, jonklaas2014ata]. The Mandel 1990 NEJM letter [mandel1990] documenting the early-pregnancy increase in thyroxine requirement was the first systematic demonstration that LT4 dose is not a static parameter, a finding extended by Alexander 2004 NEJM [alexander2004], which quantified the timing and magnitude of the necessary dose increase (40, 50% on average, by ~5 weeks gestation).

Population-level characterization advanced through the Whickham survey: Tunbridge and colleagues published the 1977 baseline cross-sectional characterization of thyroid disease prevalence in a UK community [tunbridge1977whickham], and Vanderpump's 1995 20-year follow-up [vanderpump1995whickham] established the population-level incidence of overt and subclinical thyroid disease and rate of progression from subclinical to overt hypothyroidism, approximately 4% per year in TPO-antibody-positive women with TSH >2 mIU/L. The Hollowell 2002 NHANES III analysis [hollowell2002nhanes] mapped the U.S. distribution of TSH, free T4, and thyroid antibodies and remains the primary reference for U.S. prevalence and reference range distribution. The Andersen 2002 JCEM analysis [andersen2002] of within-person versus between-person variation in serum thyroid hormones, showing that an individual's set point occupies a narrow window inside the wider population reference range, provided the biological substrate for narrow-therapeutic-index reasoning and for the clinical observation that TSH can drift out of an individual's tolerance range while still being technically 'normal'.

Reference-range debates centered on age: Surks and Hollowell [surks2007age] argued that the apparent rise in TSH with age in NHANES III represented physiologic shift rather than disease, with implications for over-diagnosis of mild subclinical hypothyroidism in older adults; the Vadiveloo TEARS analysis [vadiveloo2013tears] replicated the age-shift finding in a UK population. The cardiovascular evidence base for subclinical hypothyroidism developed in parallel: Razvi 2008 published a meta-analysis [razvi2008] showing that the association between subclinical hypothyroidism and ischemic heart disease was concentrated in adults under 65; Cappola 2006 JAMA [cappola2006] in the Cardiovascular Health Study

found no excess CHD mortality in elderly subclinical hypothyroidism; Rodondi 2010 JAMA [rodondi2010] aggregated 11 prospective cohorts (>55,000 participants) in an individual-participant-data meta and found increased CHD mortality only when TSH was ≥10 mIU/L; Selmer 2014 [selmer2014] confirmed in a nationwide Danish cohort that overt and severe subclinical hypothyroidism, but not mild SCH, drive cardiovascular mortality; Razvi 2012 [razvi2012] reported reduced ischemic events in younger SCH patients started on levothyroxine in a UK primary-care database. The clinical translation came with the TRUST trial [stott2017trust], a double-blind RCT of levothyroxine versus placebo in adults ≥65 with subclinical hypothyroidism (TSH 4.6, 19.9 mIU/L), which found no symptomatic benefit at 12 months; the Cochrane review of subclinical hypothyroidism [villar2007cochrane] had previously reported no benefit on cardiovascular events, lipids, or symptoms in pooled randomized data. The Roos 2005 RCT [roos2005] separately addressed the starting-dose question in primary hypothyroidism, showing that a full-replacement starting dose was non-inferior to incremental titration.

Pregnancy thyroid disease evidence advanced through the Negro 2010 universal screening RCT [negro2010], the Alexander 2017 ATA pregnancy management guidelines [alexander2017ata], the Korevaar Generation R analyses of maternal thyroid function and fetal/child outcomes [korevaar2013], the Lazarus 2012 CATS trial [lazarus2012cats] (which screened pregnant women for hypothyroidism and randomized to treatment versus no treatment, with no difference in child IQ at age 3), the Casey 2017 NEJM RCT [casey2017] (no neurodevelopmental benefit to treating subclinical hypothyroidism or isolated hypothyroxinemia identified in routine pregnancy screening), and the Maraka 2016 Thyroid meta-analysis [maraka2016meta] of treatment effects on pregnancy outcomes. The ETA subclinical hypothyroidism guidelines [pearce2013eta] integrate these data into stratified treatment recommendations.

Formulation pharmacology advanced through the 2000s and 2010s. Centanni and colleagues [centanni2006] demonstrated that Helicobacter pylori infection and atrophic gastritis impair levothyroxine tablet absorption, with substantial dose increases required for euthyroid maintenance, a finding extended by Liwanpo and Hershman [liwanpo2009] and the Lahner/Virili 2014 review [lahner_virili2014] to PPI use, calcium, iron, fiber, soy, and other achlorhydric states. Pabla 2009 [pabla2009] characterized the pH-dependent dissolution profile of different commercial tablets, providing the in vitro mechanism for variable absorption. Benvenga 2008 [benvenga_coffee2008] demonstrated that coffee within 60 minutes of dosing impairs tablet absorption. Vita and colleagues [vita2014] and Yue [yue2012] demonstrated that liquid-filled gel-cap (Tirosint) and oral-solution (Tirosint-SOL) formulations bypass the dissolution step and produce more reproducible serum levels in patients with malabsorption; Pirola 2018 [pirola_breakfast2018] showed equivalent TSH control with liquid LT4 taken at breakfast versus 30 minutes before. Combination L-T4/L-T3 therapy was addressed in the ETA 2012 guidelines [wiersinga2012eta], the Biondi, Wartofsky 2012 JCEM review [biondi_wartofsky2012], and the McAninch, Bianco 2015 mechanistic review [mcaninch_bianco2015]; the Akirov 2019 IPD meta of patient preference [akirov2019] frames the modest but reproducible preference signal in some series. The Klein, Ojamaa 2001 NEJM review [klein_ojamaa] and the Biondi, Klein 2004 Endocrine review [biondi_klein2004] provide the canonical cardiovascular-physiology framework. Thyroid cancer TSH-suppression dosing strategy was codified in the ATA 2009

[cooper2009ata] and ATA 2015 [haugen2015ata] management guidelines, with Biondi 2010 [biondi2010_tsh_suppression] explicitly weighing the cardiovascular and skeletal risks of long-term TSH suppression against tumor recurrence risk. FDA designated levothyroxine a narrow therapeutic index drug in 2017 [fda_nti_levothyroxine]; Hennessey 2018 [hennessey2018review] and Hennessey 2022 [hennessey2022switching] address the clinical implications of the designation and of generic-to-generic switching.

Compounded T4 (Levothyroxine) Timeline

1914 • Edward Calvin Kendall isolates crystalline thyroxine from desiccated thyroid extract at the Mayo Clinic

1926 • Harington determines the chemical structure of thyroxine as 3,5,3',5'-tetraiodothyronine

1927 • Harington and Barger synthesize thyroxine, first chemical synthesis of a thyroid hormone

1955 • Synthroid (levothyroxine sodium tablet) is FDA-approved; synthetic levothyroxine gradually displaces desiccated thyroid extract as the standard of care across the 1960s, 1970s [fda_label_synthroid]

1977 • Tunbridge, Evered, and colleagues publish the Whickham survey cross-sectional analysis of thyroid disease prevalence in a UK community, foundational epidemiology of autoimmune thyroid disease [tunbridge1977whickham]

1990 • Mandel and colleagues (NEJM) document the increased need for thyroxine during pregnancy in women with primary hypothyroidism, first systematic demonstration that LT4 dose is dynamic, not static [mandel1990]

1995 • Escobar-Morreale and colleagues (J Clin Invest) demonstrate in athyreotic rats that thyroxine alone does not restore euthyroid hormone concentrations in all tissues, biological basis for the long-running T4 monotherapy versus T4/T3 combination debate [escobar_morreale1995]

1995 • Vanderpump and colleagues publish the 20-year follow-up of the Whickham cohort, establishes population-level incidence of overt and subclinical thyroid disease and progression rates [vanderpump1995whickham]

2001 • Klein and Ojamaa publish the NEJM review on thyroid hormone and the cardiovascular system, canonical reference for cardiac contractility, heart rate, peripheral vascular resistance, and the cardiovascular consequences of over- and under-replacement [klein_ojamaa]

2002 • Hollowell and colleagues publish the NHANES III serum TSH, free T4, and thyroid antibody distribution in the US population, primary reference for US prevalence and reference range distribution; Andersen and colleagues (JCEM) demonstrate that within-person variation in serum T4 and TSH is much narrower than the population reference range, biological substrate for narrow-therapeutic-index reasoning [hollowell2002nhanes; andersen2002]

2002 • Salerno and Selva independently publish RCT and observational evidence on early high-dose levothyroxine for congenital hypothyroidism, basis for the 10, 15 mcg/kg/day starting dose still used today [salerno2002; selva2002]

2004 • Alexander and colleagues (NEJM) quantify the timing and magnitude of LT4 dose increase needed during pregnancy, 40, 50% on average, by approximately 5 weeks gestation; Biondi and Klein publish the Endocrine review on hypothyroidism as a cardiovascular risk factor [alexander2004; biondi_klein2004]

2005 • Roos and colleagues (Arch Intern Med) publish RCT demonstrating that a full-replacement starting dose of levothyroxine is non-inferior to incremental low-dose titration in primary hypothyroidism [roos2005]

2004 • Cooper publishes the JAMA scientific review on subclinical thyroid disease, frames the clinical question that the TRUST and IEMO 80+ trials would later test [cooper2004]

2006 • Centanni and colleagues publish in NEJM the demonstration that Helicobacter pylori infection and atrophic gastritis impair levothyroxine tablet absorption, basis for using liquid or soft-gel formulations in achlorhydric patients; Cappola and colleagues (JAMA, Cardiovascular Health Study) report no excess CHD mortality in elderly subclinical hypothyroidism; Olubowale and Chadwick characterize LT4 replacement dose requirements after thyroidectomy [centanni2006; cappola2006; olubowale2006]

2007 • Surks and Hollowell argue that age-related rise in TSH represents physiologic shift rather than disease, with implications for over-diagnosis of mild subclinical hypothyroidism in older adults; Cochrane review of subclinical hypothyroidism finds no clinical benefit from treatment [surks2007age; villar2007cochrane]

2008 • Razvi and colleagues publish age-stratified meta of subclinical hypothyroidism and ischemic heart disease, risk concentrated in adults under 65; Biondi and Cooper publish the Endocrine Reviews monograph on clinical significance of subclinical thyroid dysfunction; Benvenga demonstrates that coffee within 60 minutes of tablet dosing impairs LT4 absorption [razvi2008; biondi_cooper2008; benvenga_coffee2008]

2009 • Tirosint (liquid-filled soft-gel capsule, IBSA) is FDA-approved, first non-tablet branded levothyroxine in the US; Cooper and the ATA Taskforce publish revised ATA management guidelines for thyroid nodules and differentiated thyroid cancer (precursor to the 2015 Haugen guideline); Pabla and colleagues publish the pH-dissolution profile comparison of commercial LT4 tablets; Liwanpo and Hershman review absorption-interfering drugs [fda_label_tirosint; cooper2009ata; pabla2009; liwanpo2009]

2010 • Negro and colleagues publish the universal-screening-versus-case-finding RCT in pregnancy, supports the position that screening high-risk pregnant women for thyroid dysfunction improves obstetric outcomes; Rodondi and colleagues (JAMA) publish individual-participant-data meta of 11 prospective cohorts (>55,000 participants) showing CHD mortality risk concentrated at TSH ≥10 mIU/L; Biondi and Cooper review benefits versus risks of TSH suppression in differentiated thyroid cancer [negro2010; rodondi2010; biondi2010_tsh_suppression]

2011 • LaFranchi publishes JCEM update on diagnosis and treatment of neonatal hypothyroidism; Devdhar and Drooger characterize predictors of LT4 replacement dose, gender and weight dominate; age does not [lafranchi2011; devdhar2011]

2012 • AACE/ATA cosponsored clinical practice guidelines for hypothyroidism in adults published in Thyroid (Garber et al.); ETA 2012 guidelines on combination L-T4 + L-T3 published in European Thyroid Journal (Wiersinga et al.); Biondi and Wartofsky publish JCEM review on personalized combination T4/T3; Razvi 2012 (Arch Intern Med) reports reduced ischemic events in younger SCH patients started on levothyroxine; Lazarus and colleagues (NEJM, CATS trial) randomize screened pregnant women to LT4 or no treatment, no difference in child IQ at age 3 [garber2012aace; wiersinga2012eta; biondi_wartofsky2012; razvi2012; lazarus2012cats]

2012 • Yue and colleagues publish pharmacokinetics of the oral solution formulation of levothyroxine vs other available dosage forms, supports development of Tirosint-SOL [yue2012]

2013 • Pearce and colleagues publish 2013 ETA Guideline on Management of Subclinical Hypothyroidism, stratifies treatment by age, TSH magnitude, symptoms, and cardiovascular risk [pearce2013eta]

2013 • Vadiveloo and colleagues publish age- and gender-specific TSH reference intervals in Tayside, Scotland (TEARS), replicates the age-related TSH shift; Korevaar publishes Generation R analyses of maternal thyroid function and adverse obstetric outcomes [vadiveloo2013tears; korevaar2013]

2014 • ATA hypothyroidism treatment guidelines published in Thyroid (Jonklaas et al.), standard of care for adult and pediatric hypothyroidism; Vita and colleagues publish review of L-thyroxine as soft-gel capsule or liquid solution; Léger and colleagues publish European Society for Paediatric Endocrinology consensus on congenital hypothyroidism; Biondi and Wartofsky publish the Endocrine Reviews monograph on treatment with thyroid hormone; Selmer and colleagues (JCEM, nationwide Danish cohort) confirm that cardiovascular mortality risk concentrates in overt and severe subclinical disease, not mild SCH; Lahner and Virili review H [jonklaas2014ata; vita2014; leger2014; biondi_wartofsky_endocrev2014; selmer2014; lahner_virili2014]. pylori and other absorption interferences

2015 • McAninch and Bianco publish the Lancet Diabetes & Endocrinology mechanistic review on variable effectiveness of LT4 monotherapy, frames the deiodinase polymorphism / tissue-specific T3 deficit hypothesis for the subset of persistently-symptomatic patients; Hoermann, Midgley, and colleagues publish the Frontiers in Endocrinology synthesis of HPT-axis homeostasis and individualized replacement [mcaninch_bianco2015; hoermann2015]

2015 • ATA management guidelines for adult patients with thyroid nodules and differentiated thyroid cancer (Haugen et al., published 2016), codifies risk-stratified TSH suppression dosing for post-thyroidectomy thyroid cancer patients [haugen2015ata]

2016 • Tirosint-SOL (oral solution, IBSA) is FDA-approved, first oral solution levothyroxine in the US, particularly relevant for pediatric and absorption-impaired adult patients; Maraka and colleagues publish Thyroid meta-analysis of LT4 effects on pregnancy outcomes in subclinical hypothyroidism, significant reduction in pregnancy loss with treatment when TSH ≥2.5 [fda_label_tirosint_sol; maraka2016meta]

2017 • TRUST trial (Stott et al., NEJM) reports no symptomatic benefit of levothyroxine vs placebo in adults ≥65 with subclinical hypothyroidism; ATA 2017 pregnancy and postpartum thyroid disease guidelines (Alexander et al.) published; Casey et al [stott2017trust; alexander2017ata; casey2017]. publish NEJM RCT of treatment of subclinical hypothyroidism and isolated hypothyroxinemia in pregnancy

2017 • FDA designates levothyroxine a narrow therapeutic index (NTI) drug, tightens bioequivalence requirements for generic substitution [fda_nti_levothyroxine]

2018 • Hennessey and Espaillat publish current evidence review on LT4/LT3 combination; Pirola and colleagues demonstrate equivalent TSH control with liquid LT4 taken at breakfast versus 30 minutes before; Cappelli and colleagues characterize adherence patterns in hypothyroid patients [hennessey2018review; pirola_breakfast2018; cappelli_adherence2018]

2019 • Akirov and colleagues publish IPD systematic review and meta-analysis of patient preferences for combination thyroid hormone therapy [akirov2019]

2020 • Ettleson and Bianco publish JCEM review on individualized therapy for hypothyroidism, synthesizes the case for moving beyond TSH-only LT4 titration in patients with persistent symptoms [ettleson_bianco2020]

2022 • Hennessey publishes JAMA Internal Medicine commentary on considerations for generic-to-generic levothyroxine switching, operationalizes the FDA NTI framework [hennessey2022switching]

Clinical Contexts for Compounded T4 (Levothyroxine)

Overt primary hypothyroidism in adults FDA APPROVED

FDA-approved indication for manufactured levothyroxine; first-line treatment per ATA, AACE, and ETA guidelines.

Levothyroxine is the first-line treatment for overt primary hypothyroidism (TSH elevated above the reference range with free T4 below the reference range) per the ATA 2014 [jonklaas2014ata] and AACE/ATA 2012 [garber2012aace] guidelines [fda_label_synthroid]. Typical replacement dose is approximately 1.6 mcg/kg/day in adults, lower (12.5, 25 mcg starting) in elderly or cardiac-disease patients, with dose titrated to TSH within the reference range over a 6, 8 week interval per dose adjustment. The ETA 2012 guidelines [wiersinga2012eta] address combination L-T4/L-T3 therapy as an option only for selected patients who remain symptomatic on monotherapy.

Branded product: Synthroid, Levoxyl, Unithroid, Tirosint, Tirosint-SOL, generic levothyroxine

Congenital hypothyroidism in neonates and infants FDA APPROVED

FDA-approved indication; high-dose early initiation is standard of care for normal neurodevelopment.

Congenital hypothyroidism is identified through newborn screening; immediate initiation of high-dose levothyroxine (10, 15 mcg/kg/day) within the first weeks of life is required to prevent irreversible cognitive impairment [jonklaas2014ata]. Selva [selva2002] and Salerno [salerno2002] established the high-dose strategy with normalized intellectual outcomes at age 4 years. Manufactured Tirosint-SOL provides an oral solution; in patients requiring a custom strength or vehicle, compounded liquid levothyroxine may be appropriate [fda_label_tirosint_sol].

Branded product: Synthroid, Tirosint-SOL, generic levothyroxine

Hypothyroidism in pregnancy and pre-conception FDA APPROVED

FDA-approved indication; dose increases by 25, 50% required on confirmation of pregnancy.

Maternal T4 is the only source of thyroid hormone for the fetus until approximately 16 weeks gestation, and maternal hypothyroidism is associated with miscarriage, preterm delivery, and adverse neurodevelopment. The ATA 2017 pregnancy guidelines [alexander2017ata] recommend treating overt hypothyroidism in pregnancy to trimester-specific TSH targets, with prompt dose increase on confirmation of pregnancy, quantified by the Mandel 1990 NEJM letter [mandel1990] and the Alexander 2004 NEJM time-course study [alexander2004] (40, 50% increase, by ~5 weeks gestation). The Negro 2010 universal-screening RCT [negro2010] supports screening of high-risk pregnant women. The Lazarus 2012 NEJM CATS trial [lazarus2012cats] randomized 21,846 pregnant women to thyroid screening with treatment versus no screening and found no difference in child IQ at age 3, a result reinforced by the Casey 2017 NEJM trial [casey2017] in subclinical hypothyroidism and isolated hypothyroxinemia identified in routine pregnancy screening, narrowing the recommendation for universal treatment [korevaar2013]. The Maraka 2016 Thyroid meta-analysis [maraka2016meta] did show a reduction in pregnancy loss with treatment in subclinical hypothyroidism with TSH ≥2.5 mIU/L, sustaining the case for treating moderate subclinical disease and for pre-conception optimization in TPO-antibody-positive women.

Branded product: Synthroid, Tirosint, Tirosint-SOL, generic levothyroxine

TSH suppression in differentiated thyroid cancer (post-thyroidectomy) FDA APPROVED

FDA-approved indication; risk-stratified suppression dosing per ATA 2015.

Following thyroidectomy for differentiated thyroid cancer, levothyroxine is used both to replace endogenous hormone production and to suppress pituitary TSH below the reference range to reduce TSH-driven proliferation of any residual thyroid tissue [jonklaas2014ata]. The ATA 2009 Cooper guideline [cooper2009ata] and the updated ATA 2015 guideline [haugen2015ata] recommend risk-stratified TSH targets: TSH <0.1 mIU/L for high-risk patients, TSH 0.1, 0.5 for intermediate-risk, and TSH 0.5, 2.0 for low-risk patients with excellent response. Dose is typically 2.0, 2.2 mcg/kg/day, higher than full replacement, to achieve suppression. The Biondi 2010 Thyroid review [biondi2010_tsh_suppression] explicitly weighs the cardiovascular and skeletal risks of long-term TSH suppression, atrial fibrillation and accelerated bone loss in postmenopausal women, against tumor recurrence risk, supporting the de-escalation strategy in patients with excellent response. Olubowale and Chadwick [olubowale2006] characterized the practical dose-finding problem after thyroidectomy.

Branded product: Synthroid, Levoxyl, Tirosint, generic levothyroxine

Central hypothyroidism (pituitary or hypothalamic) FDA APPROVED

FDA-approved indication; titration based on free T4 rather than TSH.

In central hypothyroidism, TSH is not a reliable measure of replacement adequacy because the defect is in TSH production. Levothyroxine is titrated to free T4 in the mid-to-upper reference range per the ATA 2014 guidelines [jonklaas2014ata]. Cortisol status must be assessed and replaced first if both axes are affected, to avoid precipitating adrenal crisis with thyroid hormone replacement [garber2012aace].

Branded product: Synthroid, Tirosint, generic levothyroxine

Subclinical hypothyroidism (TSH 4.5, 10 mIU/L with normal free T4) WELL STUDIED

Gray area; treatment decision stratified by age, TSH magnitude, symptoms, antibody status, cardiovascular risk, and reproductive goals.

Subclinical hypothyroidism is not a uniformly treated condition. The TRUST trial [stott2017trust] in adults ≥65 with TSH 4.6, 19.9 mIU/L found no symptomatic, quality-of-life, or hypothyroid-symptom-score benefit from levothyroxine vs placebo over 12 months. The Cochrane review [villar2007cochrane] previously found no benefit on lipids, cardiovascular events, or symptoms. The ETA 2013 guidelines [pearce2013eta] stratify treatment recommendations by age, TSH magnitude, antibody status, symptoms, and cardiovascular risk; treatment is more strongly indicated in younger adults, TSH ≥10, positive TPO antibodies, persistent hypothyroid symptoms, or pregnancy / pre-conception. The TSH age-shift evidence [surks2007age, vadiveloo2013tears] argues against treating mild subclinical hypothyroidism in adults over 70 absent other indications. The cardiovascular evidence base, Razvi 2008 age-stratified meta [razvi2008], Razvi 2012 UK primary-care cohort [razvi2012], the Rodondi 2010 JAMA IPD meta of 11 prospective cohorts [rodondi2010], the Cappola 2006 JAMA Cardiovascular Health Study analysis [cappola2006], and the Selmer 2014 Danish nationwide cohort [selmer2014], converges on a CHD-mortality signal that concentrates in TSH ≥10 mIU/L and in adults under 65, supporting a stratified, age-conditioned treatment posture. The Biondi, Cooper 2008 Endocrine Reviews monograph [biondi_cooper2008] is the canonical synthesis [cooper2004].

Hashimoto thyroiditis with persistent symptoms on T4 monotherapy WELL STUDIED

Combination L-T4/L-T3 is considered per ETA 2012 only after monotherapy optimization; evidence base is mixed.

A minority of treated hypothyroid patients report persistent symptoms (fatigue, cognitive complaints, weight) despite biochemical euthyroidism on levothyroxine monotherapy. The ETA 2012 guidelines [wiersinga2012eta] and the Biondi, Wartofsky 2012 JCEM review [biondi_wartofsky2012] suggest a closely-monitored trial of combination L-T4 + L-T3 therapy in selected patients after monotherapy has been optimized; the McAninch, Bianco 2015 mechanistic review [mcaninch_bianco2015] articulates the deiodinase-polymorphism / tissue-specific T3 deficit hypothesis underpinning the unsatisfied-monotherapy phenomenon, building on the Escobar-Morreale rat model [escobar_morreale1995] in which T4 alone failed to restore euthyroid tissue T3 in athyreotic animals. The Ettleson, Bianco 2020 JCEM review [ettleson_bianco2020] and the Akirov 2019 IPD meta of patient preferences [akirov2019] synthesize the current case for individualized therapy. The AACE/ATA 2012 guidelines [garber2012aace] and ATA 2014 guidelines [jonklaas2014ata] take a more conservative position citing inconsistent benefit across randomized trials. Compounded T4 may have a role in this population only when an excipient or absorption issue is implicated; the broader question of combination therapy is addressed in the sister compounded-T3 brief.

Levothyroxine in patients with absorption-impairing GI conditions FDA APPROVED

FDA-approved indication; formulation choice (liquid or soft-gel) is the principal lever for variable absorption.

Tablet absorption requires gastric acid to dissolve the tablet matrix. Patients with atrophic gastritis, autoimmune gastritis, Helicobacter pylori infection, celiac disease, prior gastric bypass, or chronic PPI or H2-blocker use show reduced and variable tablet bioavailability [centanni2006, liwanpo2009, lahner_virili2014]; the Pabla 2009 pH-dissolution comparison [pabla2009] provides the in vitro mechanism. Tirosint soft-gel capsule [vita2014] and Tirosint-SOL oral solution [yue2012] bypass the dissolution step and produce more reproducible absorption, with Pirola 2018 [pirola_breakfast2018] showing equivalent TSH control on liquid LT4 even when taken at breakfast versus 30 minutes before. Coffee within 60 minutes of tablet dosing reduces absorption per Benvenga 2008 [benvenga_coffee2008]; calcium, iron, fiber, soy, bile-acid sequestrants, sucralfate, sevelamer, and lanthanum carbonate similarly impair tablet absorption and must be separated by ≥4 hours. Compounded T4 is rarely first-line in this group because Tirosint/Tirosint-SOL already address the problem; the compounded role is when even Tirosint-SOL excipients are not tolerated, or when an off-formulary concentration is required.

Branded product: Tirosint, Tirosint-SOL (preferred)

Cardiovascular risk and over- or under-replacement in older adults WELL STUDIED

Well-studied; safety target rather than indication.

Levothyroxine over-replacement (suppressed TSH without thyroid cancer indication) in older adults is associated with atrial fibrillation, accelerated bone loss with increased fracture risk in postmenopausal women, and excess all-cause and cardiovascular mortality, addressed in the Klein, Ojamaa 2001 NEJM review [klein_ojamaa] and the Biondi, Klein 2004 review [biondi_klein2004] [selmer2014]. Under-replacement is also harmful: persistent hypothyroidism produces dyslipidemia, fatigue, and contributes to cardiovascular morbidity. The TRUST trial [stott2017trust] in mild SCH and the IPD meta by Rodondi [rodondi2010] together support a conservative posture, treat overt disease and severe SCH (TSH ≥10), defer mild SCH in adults ≥65 absent other indications. The Razvi 2008 [razvi2008] and Razvi 2012 [razvi2012] data suggest the benefit-of-treatment signal in SCH is concentrated in younger adults. Compounded T4 has no specific role here, the issue is dose, monitoring, and formulation-driven absorption variability, not the compounding-versus-manufactured-product distinction [biondi_cooper2008].

Off-Label Uses of Compounded T4 (Levothyroxine)

Obesity or weight management PRECLINICAL

Off-label and not appropriate in euthyroid patients; labels carry a boxed warning against this use.

Levothyroxine is not appropriate for weight loss in euthyroid patients. The FDA-approved labels carry a boxed warning explicitly against this use because doses sufficient to produce weight loss in euthyroid people approach toxic exposure and have been associated with serious cardiovascular adverse events. RonanRx will not compound levothyroxine for a weight-loss indication [fda_label_synthroid].

FDA-Approved Uses of Compounded T4 (Levothyroxine)

Brand	Indication	Year	Route
Synthroid	Hypothyroidism, replacement or supplemental therapy in primary, secondary, or tertiary hypothyroidism (any age); pituitary TSH suppression as adjunct to surgery and radioiodine for well-differentiated thyroid cancer	1955	Oral tablet (25, 50, 75, 88, 100, 112, 125, 137, 150, 175, 200, 300 mcg)
Levoxyl	Hypothyroidism, same indications as Synthroid	2001	Oral tablet
Unithroid	Hypothyroidism, same indications as Synthroid; FDA-approved as a stand-alone NDA (rather than as a generic) in 2000	2000	Oral tablet

Brand	Indication	Year	Route
Tirosint	Hypothyroidism, replacement therapy where patients require a non-tablet formulation, including malabsorption from achlorhydria, atrophic gastritis, or excipient sensitivity	2009	Liquid-filled gelatin soft-gel capsule (13, 25, 37.5, 44, 50, 62.5, 75, 88, 100, 112, 125, 137, 150, 175, 200 mcg)
Tirosint-SOL	Hypothyroidism, oral solution formulation, useful in pediatric patients, patients with swallowing difficulty, and patients with absorption-impairing conditions	2016	Oral solution (13, 25, 37.5, 44, 50, 62.5, 75, 88, 100, 112, 125, 137, 150, 175, 200 mcg per unit-dose ampule)
Generic levothyroxine sodium tablets	Hypothyroidism, AB-rated generic substitutes to specific reference listed drugs (matching strengths only); FDA narrow therapeutic index designation since 2017 tightened bioequivalence to 90, 110%	Various (1980s, present)	Oral tablet

Levothyroxine has been FDA-approved since 1955 (Synthroid) and is one of the most-prescribed drugs in the United States. The market includes multiple branded tablets (Synthroid, Levoxyl, Unithroid, Euthyrox, Levo-T), branded non-tablet products (Tirosint soft-gel capsule, Tirosint-SOL oral solution), and AB-rated generic tablets [fda_label_tirosint_sol]. FDA designated levothyroxine a narrow therapeutic index drug in 2017, which tightened bioequivalence requirements for generic substitution from the standard ±20% range to ±10% [fda_label_synthroid; fda_label_tirosint; fda_nti_levothyroxine].

FDA-approved indications across the manufactured product set are: replacement or supplemental therapy in congenital or acquired hypothyroidism (primary, secondary, or tertiary); pituitary TSH suppression as adjunct to surgery and radioiodine therapy in management of well-differentiated thyroid cancer; and management of suppression-responsive nodular goiter (limited use) [haugen2015ata]. Use in obesity or weight loss without documented hypothyroidism is explicitly not an approved indication and the labels contain a boxed warning against this off-label use.

Compounded Compounded T4 (Levothyroxine) (503A)

Compounded levothyroxine occupies a narrow legitimate 503A niche given the breadth of the FDA-approved market. Generic levothyroxine tablets, branded Synthroid, Levoxyl, Unithroid, and the non-tablet Tirosint (soft-gel capsule) and Tirosint-SOL (oral solution) products together cover most dosing, absorption, and route needs [fda_label_tirosint_sol; vita2014; yue2012]. RonanRx compounds levothyroxine when the prescriber documents a patient-specific clinical need that the manufactured market cannot meet, specifically: (1) sensitivity to an excipient present in available commercial products (acacia, lactose monohydrate, magnesium stearate, povidone, talc, FD&C and D&C dyes, gluten in some

manufacturer lots, soy lecithin in soft-gel products), (2) a custom strength below the 25 mcg Synthroid minimum or between commercial increments (typical examples: 12.5, 18.75, 37.5 mcg, used for fine titration in narrow-tolerance patients), or (3) a liquid preparation at a concentration or vehicle not available as Tirosint-SOL [fda_essentially_a_copy, fda503a].

Excipient sensitivity is the most common indication. Tirosint and Tirosint-SOL are explicitly designed to be excipient-minimal (gelatin, glycerin, water for the soft-gel; glycerol and water for the solution), and they are the first-line alternative for excipient-sensitive patients before compounding is considered [fda_label_tirosint_sol]. When even Tirosint excipients are not tolerated, or when the manufactured products do not provide a needed strength, a compounded preparation can be made in an inert vehicle documented in the prescription.

Custom strengths are the second indication. The smallest commercially available Synthroid tablet is 25 mcg, and standard tablet increments are 12 or 13 mcg between adjacent strengths. Patients with very narrow tolerance windows, typically the elderly, post-thyroidectomy patients with brittle TSH control, and pediatric patients in transition between weight-based dosing steps, sometimes benefit from intermediate strengths (e.g., 18.75 mcg, 37.5 mcg, 62.5 mcg) that the manufactured tablet lineup does not provide. Tirosint capsules and Tirosint-SOL extend the available strength range but still do not cover every titration step [fda_label_tirosint].

Pediatric liquid preparations are the third indication. Tirosint-SOL is appropriate for many pediatric patients, but specific clinical situations, feeding-tube administration at a concentration matched to the patient's tube and flush volume, allergy to a Tirosint-SOL excipient, or a strength outside the Tirosint-SOL unit-dose lineup, may require a compounded oral suspension [fda_label_tirosint_sol]. The Selva [selva2002] and Salerno [salerno2002] congenital hypothyroidism dosing strategy depends on early high-dose accuracy and underwrites the legitimacy of liquid compounding in this population.

Compounded levothyroxine is not bioequivalent to manufactured tablets, soft-gel capsules, or oral solutions [fda_label_tirosint]. Patients switching between manufactured and compounded levothyroxine require TSH reassessment 6, 8 weeks after the switch, consistent with FDA narrow therapeutic index labeling [fda_nti_levothyroxine]. RonanRx does not fill prescriptions that read as routine substitution of compounded for manufactured product without a documented clinical reason, consistent with FDA guidance on compounded copies of commercially available drugs [fda_essentially_a_copy].

Compounded T4 (Levothyroxine) Formulations and Routes

Form	Concentration	Description
Compounded oral capsule (custom strength)	Custom, typical examples 5, 10, 12.5, 18.75, 37.5, 62.5 mcg per capsule, or other prescriber-	Hard-gelatin or vegetarian-capsule oral preparation, USP <795> nonsterile compounding, in an inert vehicle (typically microcrystalline cellulose) documented per batch. Used when the patient cannot

Form	Concentration	Description
	specified strength not available commercially	tolerate excipients in commercial products or requires a custom strength.
Compounded oral suspension / liquid (pediatric)	Custom, typically 25 mcg/mL or other prescriber-specified concentration matched to patient weight, dose, and administration route	Oral suspension prepared under USP <795> for pediatric patients requiring a non-Tirosint-SOL liquid formulation. Vehicle and beyond-use date are documented per the pharmacy's stability data.
Manufactured tablet (reference)	25, 50, 75, 88, 100, 112, 125, 137, 150, 175, 200, 300 mcg	Synthroid, Levoxyl, Unithroid, Euthyrox, and AB-rated generic levothyroxine tablets. First-line manufactured products for most patients. Variable absorption in achlorhydric states.
Manufactured soft-gel capsule (Tirosint)	13, 25, 37.5, 44, 50, 62.5, 75, 88, 100, 112, 125, 137, 150, 175, 200 mcg	Liquid-filled gelatin capsule with minimal excipients (gelatin, glycerin, water). More reproducible absorption than tablets in patients with achlorhydria, atrophic gastritis, H. pylori infection, celiac disease, or PPI use.
Manufactured oral solution (Tirosint-SOL)	Unit-dose ampules from 13 to 200 mcg	Oral solution (water and glycerol) for pediatric patients, patients with swallowing difficulty, feeding-tube administration, or absorption-impairing conditions. First-line liquid alternative before compounding is considered.

Routes used in published literature: oral.

Compounded T4 (Levothyroxine) Dosing

Route	Population	Range	Duration	Study type
Oral	Adults with overt primary hypothyroidism (replacement)	Approximately 1.6 mcg/kg/day; full replacement often 100, 150 mcg/day depending on weight; titrate to TSH within the reference range over 6, 8 weeks per adjustment	Indefinite (lifelong in most cases)	FDA-approved labeled regimen; ATA 2014 / AACE-ATA 2012 guidelines
Oral	Older adults (≥65) or patients with cardiovascular disease	Start 12.5, 25 mcg/day; titrate slowly in 12.5, 25 mcg increments every 4, 6 weeks to TSH target	Indefinite	ATA 2014 guidelines

Route	Population	Range	Duration	Study type
Oral	Pregnancy (adult with established hypothyroidism)	Increase pre-pregnancy dose by 25, 50% on confirmation of pregnancy; target trimester-specific TSH (<2.5 mIU/L first trimester; <3.0 second and third) per ATA 2017	Throughout pregnancy with TSH check every 4 weeks in first half, every 4, 6 weeks in second half	FDA-approved labeled regimen; ATA 2017 pregnancy guidelines
Oral	Neonates and infants with congenital hypothyroidism	10, 15 mcg/kg/day, started within first weeks of life	Indefinite	RCT and observational evidence (Salerno 2002, Selva 2002); ATA 2014 guidelines
Oral	Pediatric (1, 18 years, replacement)	Age- and weight-stratified: 1, 3 yr 4, 6 mcg/kg/day; 3, 10 yr 3, 5 mcg/kg/day; 10, 18 yr 2, 4 mcg/kg/day; adult dosing as growth completes	Indefinite	ATA 2014 guidelines
Oral	Post-thyroidectomy differentiated thyroid cancer (TSH suppression)	Typically 2.0, 2.2 mcg/kg/day to achieve risk-stratified TSH targets: <0.1 (high risk), 0.1, 0.5 (intermediate), 0.5, 2.0 (low risk with excellent response)	Years to indefinite, with risk-stratified de-escalation	ATA 2015 management guidelines

Doctor-prescribed and titrated. Levothyroxine is typically initiated at a full replacement dose in young adults with overt hypothyroidism without cardiovascular disease (approximately 1.6 mcg/kg/day), and at a low starting dose (12.5, 25 mcg/day) in older adults or patients with cardiovascular disease to avoid precipitating angina or arrhythmia [jonklaas2014ata; garber2012aace]. TSH is rechecked 6, 8 weeks after initiation or dose change because steady state is reached in 4, 6 weeks. The Synthroid label specifically advises against using levothyroxine for weight management; doses sufficient to produce weight loss in euthyroid people approach toxic exposure.

Levothyroxine is taken on an empty stomach, ideally 30, 60 minutes before breakfast, with water only, coffee within 60 minutes of dosing reduces tablet absorption, and food, calcium carbonate, ferrous sulfate, aluminum-containing antacids, bile-acid sequestrants, sucralfate, sevelamer, and high-fiber meals all reduce absorption [fda_label_synthroid]. An alternative bedtime regimen (taken at least 3 hours after last food) has been demonstrated to produce equivalent or better TSH control. Patients on Tirosint or Tirosint-SOL have less food and acid-suppression interference and can take the dose with somewhat more flexibility [vita2014, yue2012].

Compounded levothyroxine should mirror the manufactured-product titration approach: same starting dose for the indication, same 6, 8 week TSH check interval, same target TSH. When switching between manufactured and compounded preparations, or between compounded preparations from different lots or pharmacies, a TSH check 6, 8 weeks after the switch is required per the FDA narrow therapeutic index designation [fda_nti_levothyroxine] [centanni2006].

Compounded T4 (Levothyroxine) Safety

Levothyroxine safety is dominated by dose-related effects of over- or under-replacement rather than by intrinsic drug toxicity [23]. Under-replacement produces persistent or recurrent hypothyroidism, fatigue, weight gain, cold intolerance, constipation, dyslipidemia, and, in pregnancy, adverse obstetric outcomes. Over-replacement (TSH suppressed below the reference range without thyroid cancer indication) is associated with atrial fibrillation, accelerated bone loss and increased fracture risk in postmenopausal women, and excess all-cause and cardiovascular mortality, risks emphasized in the AACE/ATA 2012 [2] and ATA 2014 [1] guidelines, framed in the Klein, Ojamaa 2001 NEJM review [44] and the Biondi, Klein 2004 review [45], and weighed against tumor recurrence risk in the Biondi 2010 TSH-suppression review [35]. The cardiovascular-mortality signal for under-treatment of overt hypothyroidism (and severe SCH with TSH ≥10) is anchored by Rodondi 2010 [32], Cappola 2006 [33], and Selmer 2014 [34]; mild SCH does not carry the same signal in adults ≥65 per the TRUST trial [5].

Acute adverse drug reactions to levothyroxine itself are rare because the drug is bioidentical to endogenous T4. Hypersensitivity is occasionally reported and is typically attributable to excipients (lactose, FD&C dyes, povidone) rather than to levothyroxine sodium itself; symptoms include rash, urticaria, and rarely angioedema [23]. This is the population for whom Tirosint, Tirosint-SOL, or a compounded excipient-free preparation is appropriate.

Dose-titration safety considerations include the narrow therapeutic index designation [26]: small dose changes produce clinically meaningful TSH changes, and switches between manufactured products, between manufactured and compounded preparations, or between compounding pharmacies require TSH recheck [23]. Drug-drug and drug-food interactions are common and clinically meaningful, calcium, iron, PPIs, bile-acid sequestrants, sucralfate, sevelamer, and fiber reduce absorption; phenytoin, carbamazepine, rifampin, and tyrosine kinase inhibitors increase clearance or alter binding; and absorption-impairing GI conditions (atrophic gastritis, H. pylori, celiac disease, gastric bypass) reduce tablet bioavailability per Centanni [20] and necessitate dose escalation or formulation switch.

Pregnancy safety is favorable, levothyroxine is FDA pregnancy category A, the only thyroid medication with this designation, because of the well-established benefit-risk profile in maternal hypothyroidism and the minimal placental transfer of T4 at physiologic doses. Lactation is also safe; minimal levothyroxine is secreted in breast milk and breastfeeding is not affected [23]. The ATA 2017 pregnancy guidelines [15] address dose adjustment and monitoring in detail.

Contraindications

Levothyroxine is contraindicated in: untreated thyrotoxicosis from any cause; acute myocardial infarction; and uncorrected adrenal insufficiency (initiating thyroid hormone replacement before glucocorticoid replacement in panhypopituitarism or Addison disease can precipitate adrenal crisis) [1]. Known hypersensitivity to levothyroxine sodium itself is rare; documented hypersensitivity to an excipient in a specific manufactured product (e.g., lactose, FD&C dyes, povidone) is a contraindication to that specific product but not to levothyroxine sodium delivered in a different vehicle.

Use in obesity or weight loss in euthyroid patients is not an approved indication and is explicitly warned against on the manufactured-product labels [23] [1].

Drug interactions

Absorption-reducing interactions (separate by 4 hours): calcium carbonate, calcium citrate, ferrous sulfate and other iron preparations, aluminum-containing antacids, magnesium-containing antacids, bile-acid sequestrants (cholestyramine, colestipol), sucralfate, sevelamer, lanthanum carbonate, raloxifene, and high-fiber meals, comprehensively cataloged by Liwanpo and Hershman [54]. Coffee within 60 minutes of dosing reduces conventional tablet absorption per Benvenga 2008 [56]; soybean flour and walnut consumption near dosing also reduce tablet absorption. Tirosint and Tirosint-SOL are less affected by food and acid-suppression interference than conventional tablets [21][22][53], with the Pirola 2018 study [57] demonstrating equivalent TSH control even when liquid LT4 is taken at breakfast versus 30 minutes before [23].

Achlorhydric and absorption-impairing states reduce tablet bioavailability: atrophic gastritis, autoimmune gastritis, Helicobacter pylori infection, celiac disease, prior gastric bypass, prolonged PPI or H2-blocker use. Centanni [20] established that H. pylori infection and atrophic gastritis can substantially increase the levothyroxine dose required for euthyroid maintenance, and that eradication of H [23]. pylori reduces the dose requirement, extended by Lahner and Virili [55] to other H. pylori-associated absorption problems. Liquid and soft-gel formulations bypass the tablet dissolution step and are the first-line alternative in this population [21][22].

Clearance and metabolism interactions: phenytoin, carbamazepine, phenobarbital, rifampin, and sertraline can increase levothyroxine clearance. Tyrosine kinase inhibitors (sorafenib, sunitinib, imatinib) and oral estrogens (which increase TBG) can require dose escalation. Amiodarone and biotin can interfere with thyroid function test interpretation rather than levothyroxine pharmacology. Concomitant warfarin requires INR monitoring as thyroid hormone enhances vitamin K-dependent factor clearance [1].

Glucocorticoids: in panhypopituitarism or Addison disease, glucocorticoid replacement must be in place before initiating levothyroxine to avoid precipitating adrenal crisis [1].

Adverse events

Adverse events in correctly dosed patients are uncommon and largely consist of hypersensitivity to excipients in specific manufactured products (rash, urticaria, rare angioedema; addressed by switching to Tirosint, Tirosint-SOL, or a compounded excipient-free preparation). Hair loss can occur transiently during initial replacement, particularly in pediatric patients, and typically resolves with continued therapy.

Adverse events of over-replacement (iatrogenic thyrotoxicosis) are dose-related and clinically important: palpitations, tachycardia, atrial fibrillation, tremor, anxiety, insomnia, heat intolerance, weight loss, diarrhea, and in postmenopausal women accelerated bone loss with increased fracture risk. Over-replacement in older adults is associated with excess cardiovascular and all-cause mortality per multiple cohort analyses and is the primary safety target of the ATA 2014 [1] and AACE/ATA 2012 [2] dosing recommendations.

Adverse events of under-replacement (persistent hypothyroidism) are also dose-related: fatigue, weight gain, cold intolerance, constipation, dyslipidemia, depressive symptoms. Persistent under-replacement during pregnancy is associated with miscarriage, preterm delivery, and adverse fetal neurodevelopment [15][13][16].

Monitoring Compounded T4 (Levothyroxine) Therapy

Baseline assessment: TSH and free T4 to confirm hypothyroidism and characterize severity; TPO antibody status (informative for prognosis and progression risk per Vanderpump [vanderpump1995whickham]); weight (a stronger predictor of LT4 requirement than age per Devdhar 2011 [devdhar2011]); comorbidities relevant to dose selection (cardiovascular disease, pregnancy, pre-existing adrenal insufficiency, malabsorption) [garber2012aace]. The Andersen 2002 within-person versus between-person variation analysis [andersen2002] is the rationale for treating an individual's prior TSH set point, not the population mean, as the meaningful target where it is known.

On therapy: TSH every 6, 8 weeks after initiation or dose change until stable; then every 6 months for the first year; then annually if stable. In pregnancy, TSH every 4 weeks during the first half and every 4, 6 weeks during the second half per ATA 2017 [alexander2017ata], with dose increase quantified by Alexander 2004 [alexander2004] and Mandel 1990 [mandel1990]. In thyroid cancer suppression, TSH and thyroglobulin (with TgAb) per the ATA 2015 risk-stratified schedule [haugen2015ata] and the prior ATA 2009 guideline [cooper2009ata], with the Biondi 2010 review [biondi2010_tsh_suppression] framing the suppression-versus-risk trade-off in older adults and postmenopausal women [garber2012aace]. In central hypothyroidism, titrate to free T4 rather than TSH [jonklaas2014ata] [yue2012; pabla2009].

Switch between products: a TSH check 6, 8 weeks after switching between manufactured products, between manufactured and compounded preparations, or between compounding pharmacies is required, consistent with the FDA narrow therapeutic index designation [fda_nti_levothyroxine] and the Hennessey 2022 generic-to-generic switching framework [hennessey2022switching] [garber2012aace]. Switches into or out

of liquid/soft-gel formulations are particularly likely to change measured TSH because tablet absorption variability collapses on the liquid/soft-gel side [vita2014; pirola_breakfast2018].

Compounded T4 (Levothyroxine) in Special Populations

Compounded T4 (Levothyroxine) Evidence Quality

Evidence supporting levothyroxine for overt hypothyroidism is exceptionally strong: more than 60 years of clinical use, multiple FDA-approved manufactured products, and a guideline body, ATA 2014 [jonklaas2014ata], AACE/ATA 2012 [garber2012aace], and ETA 2012/2013 [wiersinga2012eta, pearce2013eta], that converges on levothyroxine monotherapy as standard of care. Pregnancy management is supported by the Alexander 2017 ATA pregnancy guidelines [alexander2017ata], the Negro 2010 universal-screening RCT [negro2010], the Korevaar Generation R analyses [korevaar2013], and the Casey 2017 NEJM RCT in subclinical pregnancy disease [casey2017]. Pediatric congenital hypothyroidism dosing is supported by Salerno [salerno2002] and Selva [selva2002] and the ATA 2014 guideline. TSH suppression dosing for differentiated thyroid cancer is codified in the ATA 2015 guidelines [haugen2015ata].

Evidence for treatment of mild subclinical hypothyroidism is mixed-to-negative: the TRUST trial [stott2017trust] in older adults and the Cochrane review by Villar [villar2007cochrane] both reported no symptomatic or cardiovascular benefit, narrowing the population for whom treatment is clearly indicated. The ETA 2013 guideline [pearce2013eta] integrates this evidence into a stratified approach.

Formulation-pharmacology evidence is well established: Centanni [centanni2006] for absorption impairment in achlorhydric states, Vita [vita2014] and Yue [yue2012] for the absorption advantage of liquid and soft-gel formulations, and the FDA narrow therapeutic index designation [fda_nti_levothyroxine] for the regulatory framework around bioequivalence and substitution.

Evidence specifically supporting compounded preparations is limited, there is no parallel efficacy program for compounded levothyroxine, and clinical use is justified case-by-case by patient-specific factors that the manufactured product cannot accommodate. Compounded preparations are not bioequivalent to manufactured tablets, soft-gel capsules, or oral solutions, and TSH reassessment is required after any switch.

Major Compounded T4 (Levothyroxine) Clinical Studies

Study	Design	Participants	Duration	Finding
		—	—	

Study	Design	Participants	Duration	Finding
Jonklaas et al. (2014, Thyroid), ATA hypothyroidism treatment guidelines	American Thyroid Association task force clinical practice guideline on thyroid hormone replacement			Levothyroxine monotherapy is the standard treatment for hypothyroidism; addresses dose, titration, special populations, and the limited evidence base for routine T4/T3 combination [jonklaas2014ata]
Garber et al. (2012, Thyroid), AACE/ATA hypothyroidism guidelines	Cosponsored AACE/ATA clinical practice guideline for hypothyroidism in adults	—	—	Levothyroxine monotherapy first-line; addresses TSH targets, generic vs branded substitution, and the narrow therapeutic index considerations [garber2012aace]
Wiersinga et al. (2012, Eur Thyroid J), ETA L-T4 + L-T3 guidelines	European Thyroid Association clinical practice guideline on combination L-T4/L-T3 therapy	—	—	Combination therapy may be considered as a closely-monitored trial in selected hypothyroid patients with persistent symptoms on monotherapy; routine use is not recommended [wiersinga2012eta]
Pearce et al. (2013, Eur Thyroid J), ETA subclinical hypothyroidism guidelines	European Thyroid Association clinical practice guideline on management of subclinical hypothyroidism	—	—	Stratified treatment recommendations by age, TSH magnitude, antibody status, symptoms, and cardiovascular risk; treatment more strongly indicated in younger adults, TSH ≥10, and pregnancy [pearce2013eta]
Stott et al. (2017, NEJM), TRUST trial	Double-blind, randomized, placebo-controlled trial of levothyroxine in adults ≥65 with subclinical hypothyroidism (TSH 4.6, 19.9 mIU/L)	737	12 months (primary endpoint); extended follow-up	No symptomatic, quality-of-life, or hypothyroid-symptom-score benefit from levothyroxine vs placebo at 1 year; supports against routine treatment of mild subclinical hypothyroidism in older adults [stott2017trust]
Villar et al. (2007, Cochrane Database Syst Rev), Subclinical	Systematic review and meta-analysis of RCTs of thyroid	—	—	No clear evidence of symptomatic, cardiovascular, or lipid benefit from levothyroxine treatment in

Study	Design	Participants	Duration	Finding
hypothyroidism Cochrane review	hormone replacement in subclinical hypothyroidism			mild subclinical hypothyroidism [villar2007cochrane]
Cooper (2004, JAMA), Subclinical thyroid disease scientific review	Scientific review and guidelines for diagnosis and management of subclinical thyroid disease	—	—	Establishes the clinical question and decision framework for subclinical hypothyroidism that the TRUST and IEMO trials would later test [cooper2004]
Tunbridge et al. (1977, Clin Endocrinol), Whickham survey baseline	Cross-sectional population survey of thyroid disease prevalence in a UK community	2779	—	Foundational characterization of community prevalence of overt and subclinical hypothyroidism and autoimmune thyroid disease antibodies [tunbridge1977whickham]
Vanderpump et al. (1995, Clin Endocrinol), Whickham 20-year follow-up	Twenty-year follow-up cohort study of the original Whickham community survey	1877	20 years	Population-level incidence of overt hypothyroidism approximately 3.5/1000/year in women and 0.6/1000/year in men; combined TPO-antibody-positive and elevated-TSH state confers approximately 4%/year progression risk to overt disease [vanderpump1995whickham]
Hollowell et al. (2002, JCEM), NHANES III thyroid analysis	Population-level analysis of serum TSH, free T4, and thyroid antibody distribution in NHANES III (1988, 1994)	17353	—	US prevalence of hypothyroidism approximately 4.6% (0.3% overt, 4.3% subclinical); primary reference for US TSH and free T4 reference range distribution [hollowell2002nhanes]
Surks and Hollowell (2007, JCEM), Age-specific TSH distribution	Re-analysis of NHANES III TSH distribution stratified by age	—	—	TSH rises modestly with age in adults free of thyroid disease; implies that the apparent rise in subclinical hypothyroidism prevalence with age may partly reflect a physiologic shift rather than disease [surks2007age]

Study	Design	Participants	Duration	Finding
Vadiveloo et al. (2013, JCEM), TEARS age- and gender-specific TSH	Population-level analysis of age- and gender-specific TSH reference intervals in a UK regional thyroid database	—	—	Confirms the age-related rise in TSH in adults free of thyroid disease; supports age-stratified reference intervals for diagnosing mild subclinical hypothyroidism [vadiveloo2013tears]
Negro et al. (2010, JCEM), Universal screening vs case finding in pregnancy	Randomized controlled trial of universal screening vs case finding for thyroid dysfunction in pregnant women	4562	—	Universal screening improved obstetric outcomes in the high-risk subset; supports screening of high-risk pregnant women for thyroid dysfunction [negro2010]
Casey et al. (2017, NEJM), Subclinical hypothyroidism in pregnancy	Randomized, double-blind, placebo-controlled trial of levothyroxine vs placebo in pregnant women with subclinical hypothyroidism or isolated hypothyroxinemia	1203	Treatment from before 20 weeks gestation; child cognitive outcome at age 5	No difference in cognitive outcome at age 5 between levothyroxine and placebo for subclinical hypothyroidism or isolated hypothyroxinemia identified in routine pregnancy screening, narrows the population for whom universal treatment is recommended [casey2017]
Korevaar et al. (2013, JCEM), Generation R hypothyroxinemia and TPO antibodies	Prospective population-based cohort analysis (Generation R) of maternal thyroid function and obstetric outcomes	—	—	Hypothyroxinemia and TPO-antibody positivity are risk factors for premature delivery; supports the case for trimester-specific TSH targets and TPO antibody assessment in pregnancy [korevaar2013]
Alexander et al. (2017, Thyroid), ATA pregnancy and postpartum thyroid guidelines	American Thyroid Association clinical practice guideline on management of thyroid disease in	—	—	Trimester-specific TSH targets, dose-increase recommendations on confirmation of pregnancy, and stratified treatment recommendations for subclinical

Study	Design	Participants	Duration	Finding
	pregnancy and postpartum			hypothyroidism in pregnancy [alexander2017ata]
Salerno et al. (2002, Thyroid), Starting doses in congenital hypothyroidism	Comparison of starting doses of levothyroxine on growth and intellectual outcome at four years in congenital hypothyroidism	—	—	Higher initial doses (12, 15 mcg/kg/day) produce better cognitive outcomes than lower starting doses; basis for the current 10, 15 mcg/kg/day starting dose in newborn-screened congenital hypothyroidism [salerno2002]
Selva et al. (2002, J Pediatr), Initial dose in congenital hypothyroidism	Observational and dose-comparison study of initial L-thyroxine dose in congenital hypothyroidism	—	—	Higher initial doses normalize TSH and free T4 more rapidly with no signal of adverse effect on growth or behavior; complementary evidence to Salerno [selva2002]
Haugen et al. (2015, Thyroid), ATA differentiated thyroid cancer guidelines	American Thyroid Association management guidelines for adult patients with thyroid nodules and differentiated thyroid cancer	—	—	Risk-stratified TSH suppression targets in post-thyroidectomy thyroid cancer: <0.1 mIU/L (high risk), 0.1, 0.5 (intermediate), 0.5, 2.0 (low risk with excellent response) [haugen2015ata]
Centanni et al. (2006, NEJM), H. pylori and atrophic gastritis impair levothyroxine absorption	Prospective study of levothyroxine dose requirements in patients with Helicobacter pylori infection or atrophic gastritis	—	—	H. pylori infection and atrophic gastritis substantially increase the levothyroxine dose required for euthyroid maintenance; eradication of H [centanni2006]. pylori reduces the dose requirement, basis for using non-tablet formulations in achlorhydric patients
Vita et al. (2014, Expert Opin Drug Deliv), Soft-gel and liquid levothyroxine	Review of clinical pharmacology and absorption data for L-thyroxine as soft-gel capsule or	—	—	Soft-gel capsule (Tirosint) and oral solution (Tirosint-SOL) bypass the tablet dissolution step and produce more reproducible absorption than tablets, particularly in patients with achlorhydria, atrophic gastritis, H

Study	Design	Participants	Duration	Finding
	liquid solution vs tablet			[vita2014]. pylori, celiac disease, or PPI use
Yue et al. (2012, Arzneimittelforschung), PK of oral solution vs other dosage forms	Pharmacokinetic comparison of oral solution levothyroxine vs other available dosage forms	—	—	Oral solution formulation produces equivalent or superior bioavailability vs tablet and soft-gel formulations, with potential advantages in absorption-impaired populations [yue2012]
Razvi et al. (2008, JCEM), Age and subclinical hypothyroidism / ischemic heart disease	Meta-analysis of cohort studies of subclinical hypothyroidism and ischemic heart disease, stratified by age	—	—	Association between subclinical hypothyroidism and ischemic heart disease is concentrated in adults under 65; supports age-stratified treatment posture [razvi2008]
Razvi et al. (2012, Arch Intern Med), Levothyroxine and CV events in subclinical hypothyroidism	Retrospective cohort of UK primary-care registry subjects with subclinical hypothyroidism	—	—	In adults aged 40, 70, levothyroxine treatment of subclinical hypothyroidism was associated with reduced fatal and nonfatal ischemic heart disease events; signal absent in adults >70 [razvi2012]
Rodondi et al. (2010, JAMA), IPD meta of subclinical hypothyroidism and CHD	Individual-participant-data meta-analysis of 11 prospective cohorts	55287	—	Subclinical hypothyroidism with TSH ≥10 mIU/L was associated with increased coronary heart disease events and mortality; risk not statistically significant at lower TSH levels, supports treating SCH primarily when TSH ≥10 [rodondi2010]
Cappola et al. (2006, JAMA), Thyroid status and CV outcomes in older adults	Prospective cohort analysis nested in the Cardiovascular Health Study	—	—	Subclinical hypothyroidism in adults ≥65 was not associated with excess CHD or all-cause mortality; supports conservative posture toward mild SCH in older adults [cappola2006]
Selmer et al. (2014, JCEM), Danish	Nationwide Danish registry	—	—	Overt hypothyroidism and severe SCH (TSH >10) drove all-cause and

Study	Design	Participants	Duration	Finding
nationwide cohort, thyroid dysfunction and CV mortality	cohort of subjects with measured TSH			cardiovascular mortality; mild SCH did not, reinforces the Rodondi 2010 IPD-meta result in a large independent cohort [selmer2014]
Biondi and Cooper (2010, Thyroid), Benefits versus risks of TSH suppression in DTC	Critical review of TSH-suppression dosing in differentiated thyroid cancer	—	—	Long-term TSH suppression is associated with atrial fibrillation and accelerated bone loss; supports risk-stratified de-escalation in excellent-response patients, codified in the ATA 2009 and ATA 2015 guidelines [biondi2010_tsh_suppression]
Cooper et al. (2009, Thyroid), ATA management guidelines for thyroid nodules and DTC	American Thyroid Association revised management guidelines (precursor to Haugen 2015)	—	—	Risk-stratified TSH suppression targets and post-thyroidectomy management; superseded by the 2015 Haugen guideline [cooper2009ata]
Roos et al. (2005, Arch Intern Med), Starting dose of levothyroxine in primary hypothyroidism	Prospective, randomized, double-blind trial of full-replacement starting dose vs incremental low-dose titration	—	—	Full-replacement starting dose (1.6 mcg/kg/day) was non-inferior to incremental titration in adults with primary hypothyroidism without cardiac disease, supports immediate full replacement in appropriate patients [roos2005]
Mandel et al. (1990, NEJM), Increased thyroxine need in pregnancy	Prospective observational study of LT4 dose requirement in women with primary hypothyroidism through pregnancy	—	—	Most pregnant women with primary hypothyroidism require a substantial increase in LT4 dose during pregnancy, first systematic demonstration that LT4 dose is dynamic, not static [mandel1990]
Alexander et al. (2004, NEJM), Timing and	Prospective observational study of weekly	—	—	LT4 requirement increases by approximately 40, 50% by gestational week 5, plateauing by

Study	Design	Participants	Duration	Finding
magnitude of LT4 increase in pregnancy	LT4 requirements in pregnant women with hypothyroidism			week 20, basis for the current 'increase dose immediately on confirmation of pregnancy' recommendation [alexander2004]
Lazarus et al. (2012, NEJM), CATS antenatal thyroid screening trial	Cluster-randomized trial of universal antenatal thyroid screening vs no screening with child IQ as primary outcome	21846	—	No difference in child IQ at age 3 between screened-and-treated vs no-screen cohorts, argues against universal screening for purely neurodevelopmental outcomes; informed the Casey 2017 NEJM result [lazarus2012cats]
Maraka et al. (2016, Thyroid), LT4 effects on pregnancy outcomes in SCH	Systematic review and meta-analysis of LT4 vs no treatment in pregnant women with subclinical hypothyroidism	—	—	LT4 treatment reduced risk of pregnancy loss in women with SCH and TSH ≥2.5 mIU/L; effect not statistically significant in lower-TSH strata, sustains case for treating moderate SCH and for pre-conception optimization [maraka2016meta]
Andersen et al. (2002, JCEM), Within-person versus between-person variation in serum thyroid hormones	Repeated-measures study of serum T4, T3, and TSH in healthy adults	—	—	Within-person variation in serum thyroid hormone concentrations is much narrower than the population reference range, biological substrate for narrow-therapeutic-index reasoning and for treating an individual's prior set point as the meaningful target [andersen2002]
Devdhar et al. (2011, Thyroid), Predictors of LT4 replacement dose	Cross-sectional analysis of LT4 doses across hypothyroid patients in a tertiary endocrinology clinic	—	—	Body weight and gender (men require higher per-kg doses) drive LT4 requirement; age does not, supports weight-based, not age-based, initial dosing [devdhar2011]
Klein and Ojamaa (2001, NEJM), Thyroid	Comprehensive review of thyroid	—	—	Canonical reference for thyroid hormone effects on cardiac

Study	Design	Participants	Duration	Finding
hormone and the cardiovascular system	hormone effects on cardiovascular physiology			contractility, heart rate, peripheral vascular resistance, and the cardiovascular consequences of over- and under-replacement [klein_ojamaa]
Biondi and Klein (2004, Endocrine), Hypothyroidism and cardiovascular risk	Review of cardiovascular consequences of hypothyroidism and over-replacement	—	—	Establishes cardiovascular physiology framework that anchors subsequent SCH-and-CHD outcome studies [biondi_klein2004]
Biondi and Cooper (2008, Endocr Rev), Clinical significance of subclinical thyroid dysfunction	Endocrine Reviews monograph on subclinical hyper- and hypothyroidism	—	—	Canonical synthesis of the SCH literature through 2008, referenced by the ATA, ETA, and AACE/ATA guidelines that followed [biondi_cooper2008]
Biondi and Wartofsky (2012, JCEM), Combination T4/T3 toward personalized replacement	Critical review of combination T4/T3 therapy	—	—	Articulates the case for individualized therapy in monotherapy-resistant patients; integrated with the ETA 2012 combination guideline [biondi_wartofsky2012]
Biondi and Wartofsky (2014, Endocr Rev), Treatment with thyroid hormone	Endocrine Reviews monograph on thyroid hormone replacement	—	—	Comprehensive treatment-of-hypothyroidism reference covering monotherapy, combination therapy, special populations, and adverse effects of over-replacement [biondi_wartofsky_endocrev2014]
McAninch and Bianco (2015, Lancet Diabetes Endocrinol), Variable effectiveness of LT4 monotherapy	Mechanistic review of why some patients remain symptomatic on LT4 monotherapy despite normalized TSH	—	—	Articulates the deiodinase-polymorphism / tissue-specific T3 deficit hypothesis as biological basis for persistently-symptomatic monotherapy patients, basis for combination T4/T3 trial in selected patients [mcaninch_bianco2015]
		—	—	

Study	Design	Participants	Duration	Finding
Ettleson and Bianco (2020, JCEM), Individualized therapy for hypothyroidism	JCEM review on T4-monotherapy alternatives and individualized therapy			Synthesizes the case for moving beyond TSH-only LT4 titration in patients with persistent symptoms; informs the joint ATA/ETA/BTA 2021 consensus [ettleson_bianco2020]
Akirov et al. (2019, Front Endocrinol), Patient preferences for combination therapy IPD meta	Systematic review and meta-analysis of patient preferences in LT4 vs LT4+LT3 trials	—	—	Modest but reproducible patient preference for combination therapy in some series; effect size sensitive to inclusion criteria and trial design [akirov2019]
Escobar-Morreale et al. (1995, J Clin Invest), Thyroxine alone does not ensure euthyroidism	Athyreotic-rat model of LT4 vs LT4+LT3 replacement with tissue-T3 measurement	—	—	Thyroxine alone failed to restore euthyroid tissue T3 concentrations in all peripheral tissues, biological basis for the combination-therapy debate [escobar_morreale1995]
Pabla et al. (2009, Eur J Pharm Biopharm), pH-dissolution profile of commercial LT4 tablets	In vitro comparative pH-dissolution profile study of selected commercial LT4 tablet products	—	—	Commercial LT4 tablets show variable dissolution as pH rises (toward neutral or alkaline), in vitro mechanism for variable in vivo absorption in achlorhydric patients [pabla2009]
Liwanpo and Hershman (2009, Best Pract Res Clin Endocrinol Metab), Conditions and drugs interfering with thyroxine absorption	Review of GI conditions, medications, and dietary factors that impair LT4 absorption	—	—	Catalog of clinically significant absorption-interfering states (atrophic gastritis, H [liwanpo2009]. pylori, PPIs, calcium, iron, fiber, soy, bile-acid sequestrants), basis for the standard 4-hour separation rule and for formulation choice
Lahner and Virili (2014, World J Gastroenterol), H. pylori and drug malabsorption	Review of H. pylori-induced atrophic gastritis and impaired drug absorption, including levothyroxine	—	—	H [lahner_virili2014]. pylori eradication restores LT4 absorption; extends the Centanni 2006 NEJM result and frames the formulation-switch versus eradication choice

Study	Design	Participants	Duration	Finding
Benvenga et al. (2008, Thyroid), Coffee and LT4 absorption	Pharmacokinetic crossover study of LT4 absorption with and without concurrent coffee	—	—	Coffee within 60 minutes of LT4 tablet dosing significantly reduces absorption, basis for the standard 'water only' instruction [benvenga_coffee2008]
Pirola et al. (2018, J Endocrinol Invest), Liquid LT4 at breakfast vs 30 min before	Prospective study of TSH control in hypothyroid patients taking liquid LT4 at breakfast versus 30 minutes before	—	—	Liquid LT4 absorption is largely insensitive to food timing, supports practical flexibility for adherence in difficult patients [pirola_breakfast2018]
Hoermann et al. (2015, Front Endocrinol), Homeostatic control of the HPT axis	Synthesis of HPT-axis homeostatic modeling and clinical implications	—	—	Argues for personalized TSH targets based on individual set-point biology rather than fixed population reference; complements Andersen 2002 [hoermann2015]
Hennessey and Espaillat (2018, Int J Clin Pract), Current evidence for LT4/LT3 combination	Narrative review of current evidence for combination thyroid hormone therapy	—	—	Synthesizes RCT, observational, and patient-preference evidence; consistent with cautious-trial posture of guideline bodies [hennessey2018review]
Hennessey (2022, JAMA Intern Med), Generic-to-generic levothyroxine switching	Editorial commentary on FDA NTI designation and generic-to-generic switching	—	—	Operationalizes the FDA NTI framework for clinical practice; supports TSH recheck after any product switch including generic-to-generic [hennessey2022switching]
Léger et al. (2014, JCEM), European consensus on congenital hypothyroidism	European Society for Paediatric Endocrinology consensus guidelines on screening, diagnosis, and management of	—	—	Codifies the high-dose early-initiation strategy validated by Salerno and Selva; standard reference outside the US [leger2014]

Study	Design	Participants	Duration	Finding
	congenital hypothyroidism			
LaFranchi (2011, JCEM), Approach to diagnosis and treatment of neonatal hypothyroidism	Review of newborn screening, congenital hypothyroidism diagnosis, and replacement strategy	—	—	Endocrine Society / ATA-aligned overview reinforcing the early high-dose initiation strategy for normal neurodevelopment [lafranchi2011]
Olubowale and Chadwick (2006, Br J Surg), LT4 replacement after thyroidectomy	Prospective study of LT4 dose requirements after total or near-total thyroidectomy for benign disease	—	—	Characterizes practical dose-finding problem after thyroidectomy, body weight is the strongest predictor of replacement requirement [olubowale2006]

Compounded T4 (Levothyroxine) Pharmacokinetics & Pharmacodynamics

Pharmacokinetics

Levothyroxine is absorbed predominantly in jejunum and upper ileum; absolute bioavailability of conventional tablets is approximately 60, 80% in fasted euthyroid adults, reduced to 40, 50% or less in patients with achlorhydria, atrophic gastritis, H [jonklaas2014ata]. pylori infection, celiac disease, or prolonged PPI use [centanni2006]. Liquid-filled soft-gel capsules (Tirosint) and oral solution (Tirosint-SOL) bypass the dissolution step required for tablet absorption and produce more reproducible bioavailability across these conditions [vita2014, yue2012]. Time to peak plasma concentration is 2, 4 hours after oral dosing; tablet absorption is reduced by food and by interfering products (calcium, iron, aluminum, fiber, bile-acid sequestrants).

Once absorbed, T4 is >99% protein-bound (thyroxine-binding globulin, transthyretin, albumin) and distributed to peripheral tissues where it is deiodinated to active T3. Serum half-life is approximately 7 days in euthyroid adults, shorter in hyperthyroidism and longer in hypothyroidism [jonklaas2014ata]. Once-daily dosing with steady state at 4, 6 weeks supports the 6, 8 week TSH check-and-titrate interval used clinically.

Levothyroxine is metabolized primarily by deiodination (the same physiologic pathway that produces T3 and rT3) and to a lesser extent by glucuronidation and sulfation. Renal clearance is minor; hepatic disease can alter thyroid binding globulin concentrations and require closer TSH monitoring [jonklaas2014ata].

Pharmacodynamics

Pharmacodynamic effects of levothyroxine are downstream of conversion to T3 and binding to nuclear thyroid hormone receptors [jonklaas2014ata]. The primary measurable PD endpoint in primary hypothyroidism is serum TSH, which is exponentially related to free T4 and changes log-linearly with small free T4 changes, the basis for using TSH as the titration target. Free T4 is the appropriate target in central hypothyroidism and during pregnancy. Symptomatic improvement (energy, weight, mood, cold tolerance) typically lags TSH normalization by weeks to months.

Over-replacement (suppressed TSH without thyroid cancer indication) produces measurable cardiovascular and skeletal PD effects: increased heart rate, increased atrial fibrillation incidence, decreased bone mineral density, and increased fracture risk in postmenopausal women [garber2012aace]. Under-replacement produces persistent hypothyroid symptoms, dyslipidemia, and, in pregnancy, adverse obstetric outcomes.

↓↑ Comparing Compounded T4 (Levothyroxine) Formulations

Manufactured tablets (Synthroid, Levoxyl, Unithroid, Euthyrox, generic levothyroxine) are first-line for most patients; they are inexpensive, AB-rated within strength, and FDA-NTI-bioequivalent within 90, 110% [fda_nti_levothyroxine] [fda_label_synthroid]. Tablet absorption requires gastric acid and is reduced in achlorhydric states [centanni2006] and by common interfering products. Branded products and AB-rated generics within a strength are generally interchangeable per the FDA NTI bioequivalence framework, though ATA/AACE recommend maintaining the same manufacturer through a refill cycle with TSH recheck after switches.

Tirosint (liquid-filled soft-gel capsule) and Tirosint-SOL (oral solution) are FDA-approved alternatives developed specifically to address absorption variability and excipient sensitivity [fda_label_tirosint; fda_label_tirosint_sol]. Both bypass the tablet dissolution step and have demonstrated more reproducible absorption than tablets in patients with achlorhydria, atrophic gastritis, H. pylori, celiac disease, and PPI use [vita2014, yue2012]. Tirosint-SOL also addresses pediatric and swallowing-difficulty populations.

Compounded preparations are appropriate only when one of the manufactured products cannot meet a documented patient-specific need: excipient sensitivity to ingredients in all available manufactured products, a custom strength below or between commercial increments, or a pediatric liquid at a concentration or vehicle not provided by Tirosint-SOL [fda_label_tirosint_sol]. Compounded preparations are not bioequivalent to manufactured products; TSH reassessment 6, 8 weeks after any switch is required.

🌡 Compounded T4 (Levothyroxine) Storage and Handling

Manufactured levothyroxine tablets are stored at controlled room temperature (20, 25°C / 68, 77°F) protected from light and moisture in the original container [fda_label_synthroid]. Tirosint capsules and Tirosint-SOL solution have similar room-temperature storage requirements per the manufacturer labeling

[fda_label_tirosint]. Compounded levothyroxine preparations are stored per the pharmacy's stability data and beyond-use date assignment under USP <795> for nonsterile compounding; refrigerated storage is typical for compounded oral suspensions to support beyond-use dating [fda_label_tirosint_sol; usp_795].

Levothyroxine is not a cold-chain product in the conventional sense, controlled room temperature storage is sufficient. Patient education should emphasize keeping the dose in the original container, away from heat and humidity, and not transferring tablets to weekly pill organizers for extended periods.

Compounded T4 (Levothyroxine) Compounding & Operations

503A compounding

Compounded levothyroxine is prepared under 503A on patient-specific prescriptions in state-licensed compounding pharmacies. RonanRx prepares oral capsules and oral suspensions per USP General Chapter <795>, the official compendial standard for nonsterile pharmaceutical compounding, with documented active ingredient sourcing, gravimetric verification, content-uniformity testing where applicable, and full lot traceability [fda503a; usp_795]. The narrow therapeutic index designation of levothyroxine [fda_nti_levothyroxine] is reflected in tightened analytical and content-uniformity controls.

Beyond-use dating, active-ingredient identity verification, and stability assessment follow USP <795> requirements. Each compounded batch is documented per state board of pharmacy retention rules with full traceability from API lot through dispensing. Active pharmaceutical ingredient is sourced from FDA-registered facilities with documented certificates of analysis [usp_795].

Pharmacist review

Each prescription for compounded levothyroxine undergoes pharmacist review prior to dispensing. The review confirms: a documented patient-specific clinical reason that the manufactured Synthroid, Levoxyl, Unithroid, Tirosint, Tirosint-SOL, or AB-rated generic products are not appropriate (excipient sensitivity, custom strength outside commercial increments, pediatric liquid not provided by Tirosint-SOL); absence of contraindications (uncorrected adrenal insufficiency, untreated thyrotoxicosis, acute MI); appropriate concomitant medication review including the absorption-interfering drug list (calcium, iron, PPIs, bile-acid sequestrants, sucralfate, sevelamer); and a prescribed regimen consistent with ATA/AACE titration unless the prescriber documents a patient-specific reason [fda503a; fda_label_synthroid].

RonanRx does not fill prescriptions for compounded levothyroxine that read as routine substitution of compounded for manufactured product without documented clinical rationale, consistent with FDA guidance on compounded copies of commercially available drugs [fda_essentially_a_copy]. We do not compound levothyroxine for off-label weight management, the labels' boxed warning against this use applies in the same way to compounded preparations as to manufactured products [jonklaas2014ata].

Quality and traceability

Active pharmaceutical ingredients are sourced from FDA-registered facilities with documented certificates of analysis. Each batch is recorded with lot numbers traceable to API source, compounding date, beyond-use date, analytical verification result where applicable, and dispensing pharmacist of record. Finished product lot records are retained per state board of pharmacy retention requirements. Narrow therapeutic index designation drives tighter content-uniformity targets than for non-NTI products.

Cold chain

Levothyroxine is not a cold-chain product. Manufactured tablets, soft-gel capsules, and oral solution are stored at controlled room temperature [fda_label_synthroid; fda_label_tirosint; fda_label_tirosint_sol]. Compounded oral suspensions may require refrigeration to support beyond-use dating; the pharmacy's stability documentation governs storage conditions, and patient education on temperature management is provided with the dispensed product.

Frequently Asked Questions About Compounded T4 (Levothyroxine)

Is compounded levothyroxine the same as Synthroid or Tirosint?

No. Synthroid, Levoxyl, Unithroid, Tirosint, and Tirosint-SOL are the FDA-approved manufactured levothyroxine products [fda_label_synthroid; fda_label_tirosint]. Compounded levothyroxine is pharmacy-prepared on a patient-specific prescription and is not bioequivalent to the manufactured products. Compounded drugs are not FDA-approved [fda503a].

When is compounded T4 actually appropriate?

Per FDA guidance on compounded drug products, compounding of a drug that is essentially a copy of an FDA-approved product is generally restricted unless the prescriber documents a patient-specific clinical need that the manufactured product cannot meet [fda_essentially_a_copy]. For levothyroxine, the three legitimate categories are: (1) sensitivity to an excipient present in all available manufactured products (lactose, dyes, gluten, soy, specific binders) where Tirosint and Tirosint-SOL are also not tolerated; (2) a custom strength below the 25 mcg Synthroid minimum or between commercial increments (12.5, 18.75, 37.5 mcg) for narrow-tolerance patients; and (3) a pediatric oral liquid at a concentration or vehicle not provided by Tirosint-SOL [fda_label_tirosint; fda_label_tirosint_sol]. Cost or preference does not qualify.

Why does the dose matter so much with levothyroxine?

FDA designated levothyroxine a narrow therapeutic index drug in 2017 because the therapeutic and toxic ranges overlap closely, small dose differences produce clinically meaningful TSH changes, and over-replacement is associated with atrial fibrillation, accelerated bone loss, and excess cardiovascular and all-cause mortality [fda_nti_levothyroxine]. The narrow therapeutic index designation tightened

bioequivalence requirements for generic substitution and is the basis for the standard recommendation to maintain the same product across refills and to recheck TSH 6, 8 weeks after any switch, between brands, between brand and generic, or between manufactured and compounded preparations [jonklaas2014ata; garber2012aace].

Why might Tirosint or Tirosint-SOL work better than a tablet for some patients?

Tablet absorption of levothyroxine requires gastric acid to dissolve the tablet matrix. In patients with low stomach acid, atrophic gastritis, autoimmune gastritis, H. pylori infection, celiac disease, prior gastric bypass, or prolonged PPI or H2-blocker use, tablet absorption is reduced and inconsistent [centanni2006]. Tirosint (soft-gel capsule) and Tirosint-SOL (oral solution) bypass this dissolution step and produce more reproducible serum levels in these patients [yue2012]. Centanni and colleagues demonstrated this with H. pylori in NEJM in 2006; Vita and Yue subsequently characterized the soft-gel and solution formulations [vita2014].

Should subclinical hypothyroidism be treated?

It depends. The TRUST trial in adults aged 65 and over found no symptomatic or quality-of-life benefit from levothyroxine versus placebo over 12 months in mild subclinical hypothyroidism [stott2017trust; villar2007cochrane; pearce2013eta]. The Cochrane review by Villar previously reached a similar null. The ETA 2013 guideline recommends stratified decision-making by age, TSH level, antibody status, symptoms, cardiovascular risk, and pregnancy plans, with treatment more strongly indicated in younger adults, TSH ≥10 mIU/L, positive TPO antibodies, persistent hypothyroid symptoms, or in women trying to conceive.

What changes during pregnancy?

Levothyroxine is FDA pregnancy category A and treatment of overt hypothyroidism is required during pregnancy. The dose typically increases by 25, 50% on confirmation of pregnancy and TSH is checked every 4 weeks in the first half of pregnancy per the ATA 2017 pregnancy guidelines [alexander2017ata]. Trimester-specific TSH targets are <2.5 mIU/L in the first trimester and <3.0 in the second and third. Universal screening of high-risk women is supported by the Negro 2010 RCT; treatment of mild subclinical hypothyroidism or isolated hypothyroxinemia identified in routine pregnancy screening did not improve child cognition in the Casey 2017 NEJM trial [negro2010; casey2017].

What are the most common side effects?

Correctly dosed levothyroxine is exceptionally well tolerated because it is bioidentical to endogenous T4. Side effects when they occur are typically from over-replacement (palpitations, tremor, anxiety, insomnia, weight loss, heat intolerance, and in postmenopausal women accelerated bone loss) or from excipient hypersensitivity (rash, urticaria, rarely angioedema), addressed by switching to Tirosint, Tirosint-SOL, or a compounded excipient-free preparation [jonklaas2014ata; garber2012aace].

Does RonanRx sell compounded levothyroxine directly to patients?

No. Compounded levothyroxine requires a patient-specific prescription written by a licensed doctor for an identified patient with a documented clinical reason that the manufactured Synthroid, Levoxyl, Unithroid, Tirosint, or Tirosint-SOL products are not appropriate, plus pharmacist review before dispensing [fda_essentially_a_copy; fda_label_synthroid]. RonanRx is not a direct-to-consumer storefront, and we do not compound levothyroxine for off-label weight loss [fda503a].

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How to Access Compounded T4 (Levothyroxine)

Compounded Compounded T4 (Levothyroxine) 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 T4 (Levothyroxine), 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)