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Drug Class Review: Oral Thyroid Hormone

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Plain Language Summary:

- Thyroid hormones are medicines used to treat thyroid conditions like low thyroid levels and thyroid growths called nodules. Low thyroid is a condition in which the body does not make enough thyroid hormone. Levothyroxine is the name of the most common medicine used to treat low thyroid. It is not helpful to use thyroid hormone in people whose lab levels may show early signs of low thyroid but who have no symptoms of low thyroid because it does not usually improve how a person feels. In people with thyroid nodules, thyroid hormone may reduce the size of the growth.
- Use of thyroid hormone may lower risk of early childbirth compared to no treatment in pregnant people who have antibodies against thyroid tissue with normal thyroid levels, but more research is needed.
- There is no difference between different types of levothyroxine. A lower dose of thyroid hormone is usually needed for people who are older or who have heart disease.
- The Pharmacy and Therapeutics Committee recommends that thyroid hormones have a designated policy and that levothyroxine tablets be available and paid for by Fee-for-service (FFS) Medicaid. Providers must explain to the Oregon Health Authority why someone needs a different form of thyroid hormone before Medicaid will pay for it. This process is called prior authorization.

Purpose for Class Review: The purpose of this review is to create a class for oral thyroid products based on high quality evidence from a recent literature search.

Research Questions:

1. What is the high-quality comparative evidence on the efficacy and harms between thyroid hormone therapies?
2. Is there evidence regarding subgroups of patients based on demographics (i.e., age, race, ethnicity, gender), socioeconomic status, other medications (drug-drug interactions), comorbidities (drug-disease interactions), for which a specific thyroid therapy is more effective or associated with fewer harms?

Conclusions:

- There were three systematic reviews and meta-analyses and two high-quality clinical practice guidelines that were included in this class review.
- There is moderate quality of evidence that levothyroxine reduces nodule volume of 50% or more when compared to placebo or no treatment (relative risk [RR] 1.57; confidence interval [CI] 1.04 to 2.38).[1] Nodule reduction can be associated with less symptoms of pain due to pressure and for cosmetic reasons. There was insufficient evidence to draw conclusions on important health outcomes, such as incidence of thyroid cancer, health-related quality of life and adverse events.

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- A Cochrane review found low quality evidence that the treatment of people who were euthyroid, who had thyroid peroxidase antibodies (TPOAb), during pregnancy was beneficial in reducing the risk of preterm birth compared to no treatment (RR 0.28; 95% CI, 0.10 to 0.80; absolute risk reduction [ARR] 19%/number needed to treat [NNT] 5/treatment duration of 30 weeks).[2]
- Treating individuals with subclinical hypothyroidism (baseline thyroid stimulating hormone [TSH] 4.4 to 12.8 mIU/L) with thyroid replacement, compared to placebo, did not improve health-related quality of life or hypothyroid symptoms based on a high-quality systematic review and meta-analysis (high quality evidence).[3] Treatment of subclinical hypothyroidism is not recommended for most patients based on recommendations from high-quality guidelines (strong recommendation based on high-quality evidence).[5] Treatment of subclinical hypothyroidism in some patients with serum TSH levels exceeding 10 mIU/L may prevent progression to overt hypothyroidism and is recommended by some guidelines.[4]
- A guideline published by the National Institute for Health and Care Excellence (NICE) recommends the use of levothyroxine first-line for the treatment of hypothyroidism.[4]
- There was insufficient evidence to recommend the use of a specific formulation of levothyroxine in preference to another.
- There is evidence for the use of lower doses of levothyroxine in patients who are elderly or in those with a history of cardiovascular (CV) disease.[4] Women and children should follow specific dosing recommendations per labeling instructions.[6,7]

Recommendations:
- Recommend at least one formulation of levothyroxine be available as a preferred product.
- After evaluation of drug costs in executive session, make levothyroxine tablets preferred and all other formulations non-preferred.

Background:
Hypothyroidism affects approximately one in every 300 persons in the United States (US).[8] Women receive a diagnosis of hypothyroid 5-10 times more than men. Low levels of thyroid are most commonly a result of iodine deficiency worldwide; however, in the U.S. autoimmune thyroiditis (e.g. Hashimoto's thyroiditis) is the primary etiology of hypothyroidism.[9] Thyroid hormones play an important role in regulating metabolism, and brain, heart, muscle and digestive function. Untreated hypothyroidism may result in increased risk of heart failure, CV mortality and adversely affect serum lipid levels.[9] Symptoms of hypothyroid vary by age but commonly include fatigue, hair loss, depression and temperature intolerance.[10] Screening and diagnosis is predominately done by measuring TSH, with treatment of patients with serum TSH levels above 10 mIU/L. Primary hypothyroidism is defined as high serum TSH concentrations and low levels of serum free thyroxine (T4).[10] A less common etiology is central hypothyroidism which occurs as a result of hypothalamic or pituitary disease with resulting low serum T4 concentrations and a serum TSH concentration that is not appropriately elevated in response. Another type of thyroid disorder is subclinical hypothyroidism. It is associated with high serum TSH levels, normal free T4 concentrations and symptoms of hypothyroidism (e.g., tiredness, constipation, and weight gain).[9] Guidelines recommend the use of thyroid hormones to treat subclinical hypothyroidism in individuals with serum TSH values exceeding 10 mIU/L. The treatment of patients with levels of 4.5 to 10 mIU/L is controversial and has not consistently demonstrated benefit or improved outcomes.[3]

In most people, hypothyroidism is chronic and requires lifelong supplementation of thyroid hormones to reach a euthyroid state (TSH levels of 0.5 to 5.0 mIU/L). Levothyroxine (tablets, soft gels, or liquid) is synthetic thyroxine and a preferred thyroid hormone used to normalize TSH levels. Levothyroxine is converted to triiodothyronine (T3), the active thyroid hormone, in the peripheral tissues.[10] Levothyroxine is dosed at 1.6 mcg/kg per day. Individuals who are older or those with coronary heart disease should have levothyroxine initiated at a lower 25-50 mcg daily dose. Those with subclinical hypothyroidism usually require less supplementation and doses of 25-75 mcg daily are often sufficient.[9] Levothyroxine should be given on an empty stomach with water, 30-60 minutes before the first meal of the day or 2 hours after the last meal of the day.[10] Use of branded levothyroxine over generic products may be preferred by some clinicians, but the

general consensus is to use a consistent formulation of levothyroxine to reduce risk of variable patient response.[9] Desiccated thyroid can be derived from porcine or bovine sources and is most commonly available as Armour® Thyroid. Desiccated thyroid has not been extensively studied and is not commonly used but remains an option for certain patients who do not respond to other types of thyroid; however, not recommended by some guidelines.[9] Liothyronine (T3) is also used in patients who remain symptomatic on levothyroxine. Serum TSH should be reevaluated at 4-6 weeks after initiating thyroid hormone therapy. There is no high-quality evidence that supports thyroid hormone supplementation in euthyroid individuals.[10] There is insufficient evidence to support combination therapy with levothyroxine and L-triiodothyronine.[9]

Outcome measures used to determine the efficacy of thyroid replacement are normalization of elevated serum TSH levels and/or T4 levels.[11] Quality of life assessments are also used, especially in the treatment of subclinical hypothyroidism. The Thyroid-Related Quality-of-Life Patient-Reported Outcome Measure (ThyPRO) is a 4-item scale with a range of 0-100, with higher scores indicative of more hypothyroid symptoms.[3] Another tool measures quality of life via an 18-item underactive thyroid-dependent quality of life (ThyDQoL) tool, comprised of a range of -9 to 3 with higher scores indicating a better quality of life.[3]

There were 823 fee-for-service (FFS) patients who received thyroid hormones last quarter. Ninety-two percent of the claims were for levothyroxine. Thyroid hormones represent a small portion of health care costs to the Oregon Health Authority (OHA).

A summary of relevant drug information is available in **Appendix 1**, which includes pharmacology and pharmacokinetic characteristics of these drugs, contraindications, warnings and precautions, including any FDA Black Box Warnings and Risk Evaluation Mitigation Strategies.

Table 1. Indications and Dosing.

Generic Drug Name	Indication(s)	Strength/Route	Dose and Frequency+
Levothyroxine capsules, tablets and solution[10]	Hypothyroidism and pituitary thyrotropin suppression	13 - 200 mcg oral tablets and capsules (brand dependent) Oral solution 13-200 mcg/mL	Dose titrated to effect once daily (TSH levels)
Liothyronine tablets[10]	Hypothyroidism, pituitary thyrotropin suppression and thyroid suppression test	5, 25, and 50 mcg oral tablets	Dose titrated to effect once daily (TSH levels and T3 levels)
Thyroid, pork tablets*	As a replacement supplement for patients with hypothyroidism of any etiology except for transient hypothyroidism during the recovery phase of acute thyroiditis.	15-300 mg oral tablets	Starting dose of 30 mg once daily and titrated to effect

Key: * Labeling has not been approved by FDA; + TSH should be monitored every 4-6 weeks during dose titration
Abbreviations: mcg – microgram; mg – milligram; mL – milliliter; T3 – triiodothyronine; TSH – thyroid stimulating hormone

Methods:
A Medline literature search for new systematic reviews and randomized controlled trials (RCTs) assessing clinically relevant outcomes to active controls, or placebo if needed, was conducted. The Medline search strategy used for this review is available in **Appendix 2**, which includes dates, search terms and limits used. The OHSU Drug Effectiveness Review Project, Agency for Healthcare Research and Quality (AHRQ), National Institute for Health and Clinical Excellence

(NICE), Department of Veterans Affairs, and the Canadian Agency for Drugs and Technologies in Health (CADTH) resources were manually searched for high quality and relevant systematic reviews. When necessary, systematic reviews are critically appraised for quality using the AMSTAR tool and clinical practice guidelines using the AGREE tool. The FDA website was searched for new drug approvals, indications, and pertinent safety alerts.

The primary focus of the evidence is on high quality systematic reviews and evidence-based guidelines. Randomized controlled trials will be emphasized if evidence is lacking or insufficient from those preferred sources.

Systematic Reviews:

Cochrane – Levothyroxine or Minimally Invasive Therapies for Benign Thyroid Nodules

The focus of a 2014 Cochrane review evaluated the use of levothyroxine, or other treatments, for reducing the size of benign thyroid nodules.[1] Thyroid nodules are common and rarely cancerous. Nodules are problematic due to pressure symptoms or because of cosmetic concerns. The use of levothyroxine for nodule reduction was compared to placebo, or to no therapy, as well as the use of other minimally invasive therapies. Thirty-one studies (n=2083) were identified. All patients were euthyroid and most were female. Participant ages ranged from 18 to 69 years. Sixteen studies, lasting 6 months to 5 years, evaluated levothyroxine specifically. Six studies compared levothyroxine to no therapy and eight studies were placebo comparisons. Doses of levothyroxine ranged from 1 mcg/kg/day to 3 mcg/kg/day. Goal TSH levels were less than 0.01 mIU/L to 0.2 to 0.8 mIU/L (.[1]

There was insufficient evidence to draw strong conclusions on the effect of levothyroxine on the incidence of thyroid cancer, health-related quality of life and adverse events. Nodule reduction (greater than 50%) was greater with levothyroxine compared to no treatment or placebo, 16% vs. 10% (RR 1.57; CI 1.04 to 2.38; $p<0.05$), based on moderate evidence.[1]

Cochrane – Interventions for Clinical and Subclinical Hypothyroidism Pre-pregnancy and During Pregnancy

Management of clinical and subclinical hypothyroidism throughout pregnancy was the focus of a 2013 Cochrane review.[2] Studies evaluating the use of levothyroxine compared to placebo or active treatment were eligible for inclusion. Four trials with 362 women who were pregnant and euthyroid with TPOAb were included in the review. Trials were found to have moderate risk of bias.[2] Outcomes of interest were pre-eclampsia, premature birth, miscarriages and cognitive delay in newborns.

One trial (n=115) found treatment with levothyroxine, compared to no treatment did not significantly reduce the risk of pre-eclampsia in women who were euthyroid but had thyroid peroxidase antibodies (RR 0.61; 95% CI, 0.11 to 3.48).[2] Preterm birth was reduced more in with levothyroxine treatment compared to placebo in this population by 72% (RR 0.28; 95% CI, 0.10 to 0.80) (low quality of evidence).[2] There was insufficient evidence to determine the effect of levothyroxine on other outcomes.

Feller, et al – Association of Thyroid Hormone Therapy with Quality of Life and Thyroid-Related Symptoms in Patients with Subclinical Hypothyroidism

A 2018 systematic review and meta-analysis evaluated the role of treating subclinical hypothyroidism.[3] Twenty-one randomized controlled trials (RCTs) (n=2192), durations lasting from 3-18 months, met inclusion criteria. Comparisons were between thyroid hormone therapy and placebo, or no therapy, in participants who were not pregnant and had a diagnosis of subclinical hypothyroidism. Mean ages ranged from 32-74 years with women representing 46-100% of participants.[3] Mean TSH levels at baseline were 4.4 to 12.8 mIU/L and participants reported symptoms ranging from mild to moderate.[3] The primary outcomes of interest

were quality of life and thyroid-related quality of life/hypothyroid symptoms. Quality of life was scores were based on several different assessments including general health Questionnaire (GHQ-30), 18-Item ThyDQoL, and ThyPRO.

Treatment with thyroid hormone resulted in normalization in thyrotropin values (0.5-3.7 mIU/L) compared to placebo (4.6-14.7 mIU/L).[3] There was no difference between groups in general quality of life (standard mean difference [SMD] -0.11; 95% CI, -0.25 to 0.03, I^2= 66.7%).[3] Thyroid-related quality of life/hypothyroid symptoms scores were also similar between groups with a SMD of 0.01 (95% CI, -0.12 to 0.14; I^2 = 0%).[3] There was no strong evidence that thyroid replacement resulted in improved outcomes in patients with subclinical hypothyroidism.

After review, 17 systematic reviews were excluded due to poor quality (e.g., network meta-analyses), wrong study design of included trials (e.g., observational), comparator (e.g., no control or placebo-controlled), or outcome studied (e.g., non-clinical).[12–17,17–28]

Guidelines:
High Quality Guidelines:

<u>NICE – Thyroid Disease: Assessment and Management</u>
NICE updated their guidance in 2019 for the use of levothyroxine in the management of thyroid disease.[4] Treatment with levothyroxine is recommended for individuals with hypothyroidism. Obtaining goal TSH levels may take up to 6 months in individuals with very high levels at initiation. TSH should be measured every 3 months until levels have stabilized and then checked annually.[4] Patients that remain symptomatic after starting levothyroxine may benefit from measurement of free T4 as well as TSH levels.[4] Measurement of free T4 and TSH can be valuable for children ages 2 years and older and young people. Testing should be done every 6 to 12 weeks until TSH levels have normalized and then every 4 to 6 months till after puberty. After puberty, testing is recommended annually.[4] For children under the age of 2 years, the recommendation is to measure free T4 and TSH levels every 4 to 8 weeks until normalization, then every 2 to 3 months during the first year of life and every 3 to 4 months during the second year of life.[4]

NICE treatment recommendations for hypothyroidism are as follows:

- Levothyroxine is recommended first-line for adults, children and young people with primary hypothyroidism.
    - Initiate levothyroxine at a dose of 1.6 mcg/kg (round to nearest 25 micrograms) for adults under 65 years old with primary hypothyroidism and no history of CV disease.[4]
    - For adult patients with history of CV disease and are 65 years and older, consider starting levothyroxine at 25 to 50 mcg per day with titration.[4]
- Liothyronine is not routinely recommended because there has been no evidence of benefit over levothyroxine and long-term harms are unknown.
- Natural thyroid is not recommended due to lack of evidence.
- Levothyroxine can be considered for all adults with subclinical hypothyroidism (TSH of 10 mIU/L or higher on 2 separate occasions 3 months apart). Dosing should follow the same recommendations as those for hypothyroidism.[4]
- Levothyroxine can also be considered for adults under 65 years with subclinical hypothyroidism with a TSH above the reference range but lower than 10 mIU/L on 2 separate occasions 3 months apart and symptoms of hypothyroidism.
- Children and young people over the age of 2 years may also be treated with levothyroxine for subclinical hypothyroidism. Considerations should be for children with the following: TSH level of 20 mIU/L or higher, TSH between 10 and 20 mIU/L on 2 separate occasions 3 months apart or TSH between 5 and 10 mIU/L on 2 separate occasions 3 months apart with thyroid dysgenesis or signs and symptoms of thyroid dysfunction.
- Children under that age of 2 years with TSH levels of 10 mIU/L or higher with subclinical hypothyroidism are also candidates for levothyroxine.

Bekkering, et al – Thyroid Hormones Treatment for Subclinical Hypothyroidism: A Clinical Practice Guideline

A 2019 practice guideline on the treatment of subclinical hypothyroidism was developed by the British Medical Journal and the MAGIC group, who uses GRADE methodology to develop web-based guidelines. Recommendations and guidance was based off of a high-quality systematic review and meta-analysis by Feller, et al (described above).[5] Recommendations were based on the GRADE approach. No authors had conflicts with industry. Guidance pertains to individuals with subclinical hypothyroidism; defined as elevated TSH levels with normal T4 levels.

There is a strong recommendation against the use of thyroid hormone to treat subclinical hypothyroidism.[5] This recommendation is based on high-quality evidence that there was no difference between thyroid hormone supplementation and no treatment, in patients 65 years and older with subclinical hypothyroidism for the following outcomes: general quality of life, thyroid-related symptoms, fatigue/tiredness, depressive symptoms and cognitive symptoms.[5] There was low quality of evidence that there was no difference between treatment and no treatment for the outcomes of mortality and CV event. For individuals 65 years and younger, there is moderate to high quality evidence that there was no important difference between thyroid hormone and no treatment benefit for the following outcomes: general quality of life, thyroid-related symptoms, fatigue/tiredness and depressive symptoms.[5]

Additional Guidelines for Clinical Context:

ATA/AACE – Clinical Practice Guidelines for Hypothyroidism in Adults: Cosponsored by the American Association of Clinical Endocrinologists and the American Thyroid Association

In 2012 the American Thyroid Association (ATA)/American Association of Clinical Endocrinologists (AACE) released new guidance on the management of hypothyroidism.[9] The literature search and evidence evaluation was consistent with the AACE Protocol for Standardized Production of Clinical Guidelines. The evidence was graded using grades A to D, with A representing high-quality evidence and D representing expert opinion. The strength of the recommendation were also given a “best evidence” rating level (BEL) ranging from 1-4, with a level 1 recommendation being based on prospective RCTs and a level 4 determined by expert opinion.[9] Two authors had conflicts of interest. Specifics on how the systematic review was conducted was not described, and therefore, the guidelines will be used for context only.

Treatment of hypothyroidism is recommended for individuals with TSH levels greater than or equal to 10 mIU/L (Grade B, BEL 1).[9] Target TSH ranges, for non-pregnant patients, are dependent on testing and should be within the normal range of a third-generation TSH assay. In general, a range of 0.45-4.12 mIU/L should be targeted if an upper limit of normal range of a third generation TSH assay is not available (Grade B, BEL 2).[9] Patients who qualify for treatment should be initiated on levothyroxine monotherapy (Grade A, BEL 1). Levothyroxine 50 mcg daily is recommended for patients 50 to 60 years without evidence of coronary heart disease (Grade D, BEL 4).[9] Individuals with subclinical hypothyroidism should be considered for levothyroxine 25 to 75 mcg daily (Grade B, BEL 2).[9] Levothyroxine should be taken 30-60 minutes before breakfast or at bedtime 4 hours after the last meal. There is insufficient evidence to recommend the use of combination therapy with levothyroxine and L-triiodothyronine (Grade B, BEL 1). Desiccated thyroid is not recommended for the treatment of hypothyroidism (Grade D, BEL 4).[9] Interruptions in therapy lasting less than 6 weeks can be restarted at previous dose of levothyroxine, with the exception of patients with a cardiac event or marked weight loss (Grade D, BEL 4). In patients with central hypothyroidism, serum free T4 should be used to guide therapy, and levothyroxine should be titrated to increase serum T4 to mid-normal range for the assay (Grade B, BEL 3).[9] Serum TSH should be reevaluated every 4-8 weeks upon initiation of levothyroxine, to obtain TSH values within the normal range (Grade A, BEL 1).[9]

Target TSH levels for people who are pregnant should be based on trimester and are the following upper-normal reference ranges : 1st trimester, 2.5 mIU/L; second trimester 3.0 mIU/L; third trimester 3.0 mIU/L (Grade C, BEL 2).[9] Women of childbearing age should be treated with levothyroxine if they have TSH levels between 2.5 mIU/L and the upper limit of normal if they are planning on becoming pregnant or in the first trimester of pregnancy. Levothyroxine is recommended for people in the second trimester of pregnancy with a TSH between 3.0 mIU/L and the upper limit of normal or in the third trimester of pregnancy with a TSH between 3.5 mIU/L and the upper limit of normal (Grade B, BEL 2).[9] People that have positive serum TPOAb levels and are pregnant or planning on becoming pregnant should be considered for levothyroxine treatment, especially if there is a history of hypothyroidism or miscarriage (Grade B, BEL 2).[9] Levothyroxine is also recommended for people who are pregnant or planning on becoming pregnant who have positive levels of TPOAb and a TSH more than 2.5 mIU/L (Grade B, BEL 2).[9]

American Thyroid Association – Guidelines for the Treatment of Hypothyroidism

ATA released guidance on treating hypothyroidism in 2014.[11] The task force systematically reviewed the literature and graded the evidence. Grading of the evidence was done via the American College of Physicians' Guideline Grading System, with quality of evidence rated as low, medium or high. The strength of the evidence recommendation was used to assign a clinical recommendation ranging from strong to weak or no recommendation if there was insufficient evidence.[11] Two of the nine authors had industry relations. Specific methodology related to the systematic review was not described, and details on included evidence were lacking. Therefore, the guideline will be considered for clinical context only.

Table 2. ATA Recommendations for the Treatment of Hypothyroidism.[11]

Recommendation	Strength or Recommendation	Quality of Supporting Evidence
Levothyroxine is the preferred treatment for hypothyroidism.	Strong	Moderate
Clinical goals of levothyroxine therapy are resolution of hypothyroid symptoms, normalization of serum TSH and avoidance of overtreatment.	Strong	Moderate
Adherence to either brand or the same generic formulations of levothyroxine is advised to avoid variability in dose.	Weak for general population Strong for frail patients, high-risk thyroid cancer patients, and pregnant patients Strong for early childhood hypothyroidism	Low Low Moderate
Levothyroxine should be taken either 60 minutes before breakfast or at bedtime 3 or more hours after the evening meal for optimal, consistent absorption.	Weak	Moderate
Levothyroxine should be separated from medications and supplements (e.g., calcium carbonate and ferrous sulfate) that may interact by 4 hours.	Weak	Weak
Initial levothyroxine doses should be based on patient characteristics such as pregnancy, presence of cardiac disease, weight, lean body mass, etiology of hypothyroidism, degree of TSH elevation, and age.	Strong	Moderate

Serum TSH levels should be evaluated 4-6 weeks after any dosage change. Titration of levothyroxine dose should be gradual.	Strong	Moderate
Higher serum TSH levels may be targeted in elderly patients (e.g., those over 65 years).	Strong	Moderate
Women who are pregnant should receive levothyroxine with doses titrated to the appropriate level according to trimester of pregnancy. Serum TSH levels should be evaluated every 4 weeks during the first half of pregnancy. For women already taking levothyroxine, two additional doses per week of current dose may be started after confirmation of pregnancy.	Strong	Moderate
Levothyroxine 10-15 mcg/kg/day should be initiated in newborns who test positive for overt hypothyroidism with a goal of normalizing serum thyroxine in 2-4 weeks. Surveillance testing of serum TSH and T4 should occur every 1-2 months during the first year of life once the proper dose is determined. All children with overt hypothyroidism should be treated with levothyroxine.	Strong	High
Patients with secondary hypothyroidism should have a treatment goal of maintaining serum free T4 values in the upper half of the reference range.	Strong	Moderate
The use of levothyroxine to treat individuals with nonspecific symptoms and normal biochemical studies is not recommended.	Strong	High
Levothyroxine is not recommended for patients with depression who are euthyroid.	Weak	Low
Levothyroxine should not be used to treat obesity in individuals who are euthyroid.	Strong	Moderate
The treatment of urticaria with levothyroxine in euthyroid patients is not recommended.	Strong	Moderate
Levothyroxine is recommended over thyroid extracts for patients with primary hypothyroidism.	Strong	Moderate
Combination treatment with levothyroxine and liothyronine is not recommended for primary hypothyroidism.	Weak	Moderate

After review, seven guidelines were excluded due to poor quality or updated high quality guidance available.[9,11,29–33]

Randomized Controlled Trials:

A total of 1783 citations were manually reviewed from the initial literature search. After further review, all randomized controlled trial citations were excluded because of wrong study design (eg, observational), comparator (eg, no control or placebo-controlled), or outcome studied (eg, non-clinical).

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Appendix 1: Specific Drug Information

Generic	Brand	Form
levothyroxine sodium	LEVOTHYROXINE	CAPSULE
levothyroxine sodium	TIROSINT	CAPSULE
levothyroxine sodium	THYQUIDITY	SOLUTION
levothyroxine sodium	TIROSINT-SOL	SOLUTION
levothyroxine sodium	EUTHYROX	TABLET
levothyroxine sodium	LEVO-T	TABLET
levothyroxine sodium	LEVOTHYROXINE SODIUM	TABLET
levothyroxine sodium	LEVOXYL	TABLET
levothyroxine sodium	SYNTHROID	TABLET
levothyroxine sodium	UNITHROID	TABLET
liothyronine sodium	CYTOMEL	TABLET
liothyronine sodium	LIOTHYRONINE SODIUM	TABLET
thyroid, pork	ARMOUR THYROID	TABLET
thyroid, pork	NP THYROID	TABLET

Table 3. Clinical Pharmacology and Pharmacokinetics.

Drug Name	Mechanism of Action	Absorption	Metabolism/Excretion	Pharmacokinetics (mean)
Levothyroxine (T4)[6]	Levothyroxine is synthetic T4 that exerts the same physiological effect as endogenous T4. Triiodothyronine (T3) and L-thyroxine (T4) diffuse into the cell nucleus and bind to thyroid receptor proteins attached to DNA. This hormone nuclear receptor complex activates gene transcription and synthesis of messenger RNA and cytoplasmic proteins. The physiological actions of thyroid hormones are produced predominantly by T3, the majority of which (approximately 80%) is derived from T4 by deiodination in peripheral tissues.	Gastrointestinal 40-80% (T4 absorption is increased by fasting)	Metabolism is by sequential deiodination predominately via the liver and via conjugation with glucuronides and sulfates. Elimination is primarily via the kidneys (80%).	• Half-life: 6-7 days • Cmax: Not reported • AUC: Not reported • Vd: 99.96% protein bound
Liothyronine (T3)[7]	Triiodothyronine (T3) and L-thyroxine (T4) diffuse into the cell nucleus and bind to thyroid receptor proteins attached to DNA. This hormone nuclear receptor complex activates gene transcription and synthesis of messenger RNA and cytoplasmic proteins. The physiological actions of thyroid hormones are produced predominantly by T3, the majority of which (approximately 80%) is derived from T4 by deiodination in peripheral tissues.	95% absorbed within 4 hours	Metabolism is by sequential deiodination predominately. Around 80% of circulating T3 is derived from peripheral T4 monodeiodination. Conjugation is responsible for a small amount of metabolism.	• Half-life: 2.5 days • Cmax: Not reported • AUC: Not reported • Vd: 99.5% protein bound

Thyroid, pork (T3 and T4)[34]	Triiodothyronine (T3) and L-thyroxine (T4) diffuse into the cell nucleus and bind to thyroid receptor proteins attached to DNA. This hormone nuclear receptor complex activates gene transcription and synthesis of messenger RNA and cytoplasmic proteins. The physiological actions of thyroid hormones are produced predominantly by T3, the majority of which (approximately 80%) is derived from T4 by deiodination in peripheral tissues.	95% absorbed within 4 hours	Deiodination in the liver, kidney and other tissues	• Half-life: 2.5 days • Cmax: Not reported • AUC: Not reported • Vd: 99% protein bound

Use in Specific Populations:

Drug Safety:

Use in Specific Populations[6,7]:

- Elderly: initiate thyroid hormone at reduced doses, 12.5 to 25 mcg per day.
- Underlying cardiac disease: initiate thyroid hormone at reduced doses, 12.5 to 25 mcg per day.
- Pediatrics: thyroid doses should be dosed on body weight. Newborns at risk for cardiac failure and children at risk for hyperactivity should receive a lower starting dose.
- Pregnancy: thyroid doses may need to be increased during pregnancy based on serum TSH and free T4 levels.

Drug Interactions:[6,35]

- Oral anticoagulants
- Midodrine or drugs that increase blood pressure
- Drugs that may decrease T4 absorption: phosphate binders, orlistat, bile acid sequestrants, proton pump inhibitors, sucralfate, antacids.
- Drugs that may alter T4 and T3 serum transport without affecting free T4 concentrations: clofibrate, estrogen containing oral contraceptives, estrogen, heroin, methadone, 5-flourouracil, mitotane, tamoxifen , androgens, asparaginase, glucocorticoids, and slow-release nicotinic acid.
- Drugs that may transiently increase free T4: salicylates, carbamazepine, furosemide, heparin, hydantoins, non-steroidal anti-inflammatory drugs and fenamates.
- Drugs that may alter hepatic metabolism: phenobarbital and rifampin.
- Drugs that may decrease conversion of T4 to T3: beta-adrenergic antagonists, glucocorticoids and amiodarone.
- Thyroid hormones may decrease the effect of digitalis glycosides.

Boxed Warnings:
There is a FDA black box warning against the use of levothyroxine for the treatment of obesity or weight loss. Doses exceeding daily hormonal requirements may result in serious or life-threatening manifestations of toxicity.[6,7,35]

Risk Evaluation Mitigation Strategy (REMS) Programs:
There are no REMS programs for thyroid hormones.

Contraindications:
Levothyroxine should not be used in individuals with uncorrected adrenal insufficiency and in untreated thyrotoxicosis.[6,7,35]

Table 4. Summary of Warnings and Precautions.

Warning/Precaution	Levothyroxine[6]	Liothyronine[7]	Thyroid, pork[35]
Increased risk of cardiac adverse reactions in the elderly and in patients with underlying cardiovascular disease	X	X	X
Oral products should not be used to treat myxedema coma	X	X	X
In individuals with acute adrenal crisis and concomitant adrenal insufficiency, replacement glucocorticoids should be used as initial treatment before initiation of thyroid hormone treatment	X	X	X
Worsening of glycemic control	X	X	X
Decreased bone mineral density associated with thyroid hormone over-replacement	X	X	X
Prevention of hyperthyroidism or incomplete treatment of hypothyroidism by proper dose titration and ongoing monitoring due to a narrow therapeutic index. Close monitoring is recommended.	X	X	X

Appendix 2: Medline Search Strategy

Database(s): **Ovid MEDLINE(R) ALL** 1946 to May 06, 2022

Search Strategy:

#	Searches	Results
1	levothyroxine.mp. or Thyroxine/	40489
2	liothyronine.mp. or Triiodothyronine/	26163
3	thyroid.mp. or Thyroid Gland/	229285
4	hypothyroid.mp.	9689
5	1 or 2 or 3 or 4	249664
6	limit 5 to (english language and humans and yr="2012 -Current")	50111
7	limit 6 to (clinical trial, phase iii or clinical trial, phase iv or guideline or meta analysis or practice guideline or "systematic review")	1783

Appendix 3: Key Inclusion Criteria

Population	Individuals with hypothyroidism
Intervention	Thyroid hormone
Comparator	Placebo or active treatment
Outcomes	Normalization of thyroid activity and symptom reduction
Timing	NA
Setting	Outpatient