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TREATMENT/MANAGEMENT OF PEDIATRIC THYROID CONDITIONS

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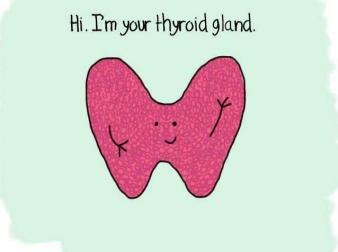

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DISCLOSURE

- I HAVE NO FINANCIAL DISCLOSURES

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OBJECTIVES

1. DESCRIBE THE FUNCTION/ROLE OF THE THYROID GLAND
2. DISCUSS COMMON PEDIATRIC THYROID CONDITIONS
3. EXPLAIN TREATMENT WITH THYROID HORMONE
4. IDENTIFY THE FORMS AND PROPER ADMINISTRATION OF THYROID HORMONE
5. DISCUSS TREATMENT WITH ANTITHYROID MEDICATION
6. DESCRIBE TREATMENT OF THYROID CANCER

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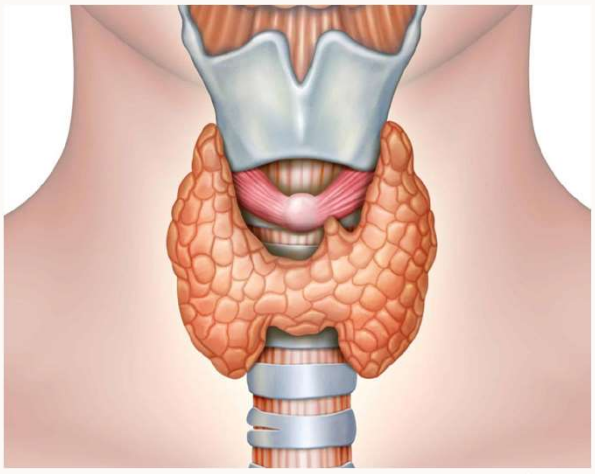
THYROID GLAND

- Butterfly-shaped endocrine gland located at the base of the neck
- The thyroid gland's main job is to make thyroid hormone, which is released into the blood stream and carried to every tissue in the body
- Thyroid hormone is responsible for controlling the speed of your body's metabolism
- In children, it is essential for:
  - ✓ **Brain development**
  - ✓ **Linear growth**
  - ✓ **Meeting developmental milestones**



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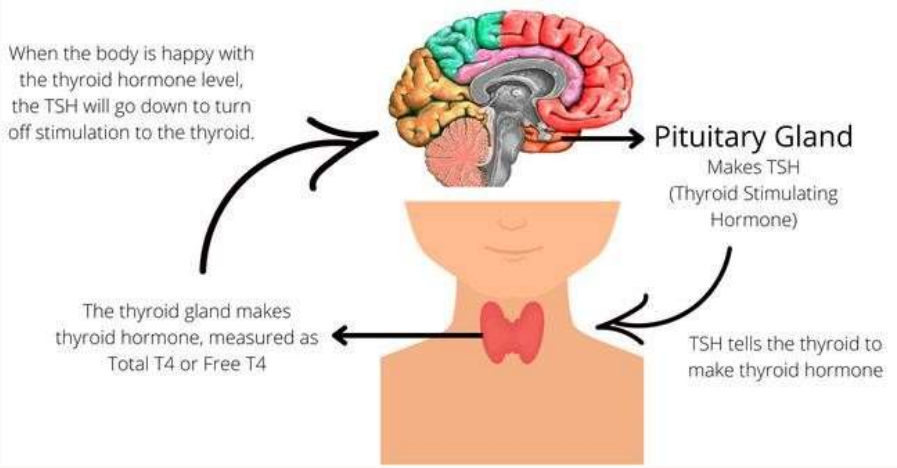
THYROID GLAND



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COMMON PEDIATRIC THYROID CONDITIONS

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CONGENITAL HYPOTHYROIDISM

- Congenital Hypothyroidism describes a condition where an infant is born with low thyroid hormone production. One in every 2,000-4,000 babies is born with congenital hypothyroidism.
- *Newborn screening* detects low thyroid function, which is then confirmed with a blood sample. Once low thyroid function is confirmed, treatment is started immediately to replace the low thyroid hormone levels.

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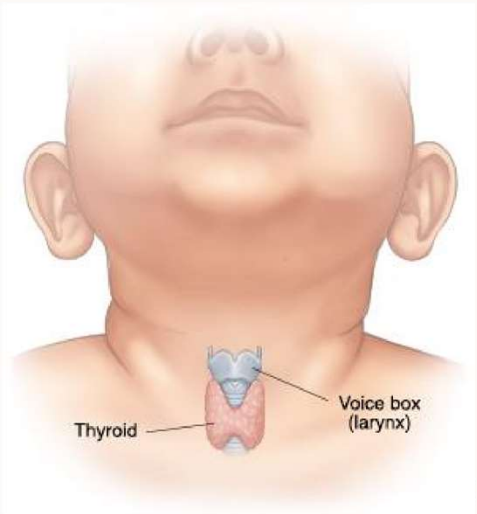
CONGENITAL HYPOTHYROIDISM

- In about 85% of infants, congenital hypothyroidism is due to an abnormally developed thyroid gland--the thyroid can be completely absent, partially absent, small, or located in an abnormal position (ectopic).
- In 10-15% of cases, the thyroid gland is present, but the hormones cannot be produced normally.
- Occasionally, infants have congenital hypothyroidism because the brain is not making TSH, which signals the thyroid to produce thyroid hormone.



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CONGENITAL HYPOTHYROIDISM

- Clinical presentation:
  - Prolonged jaundice, cold and mottled skin, large tongue, umbilical hernia, facial puffiness, open posterior fontanelle
  - Lethargy, poor feeding, constipation
- Confirmatory testing:
  - TSH >40 on initial NBS, followed by confirmatory serum TSH (high) and Free T4 (low)
  - Thyroid Ultrasound

Treatment:
- Levothyroxine 10-15mcg/kg/d

Follow-up:
- Serum TSH and Free T4 monthly until 6 months old, every 1-2 months until 12mo, every 3-4 months until 3 years old
- Clinic follow-up every 4-6 months

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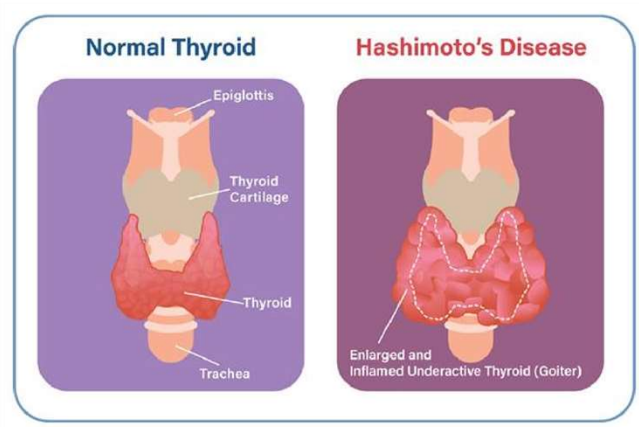
HASHIMOTO'S HYPOTHYROIDISM

- *Autoimmune thyroiditis*
- The immune system mistakes thyroid gland cells and their enzymes for invaders and can attack them, resulting in few healthy thyroid cells left to make enough thyroid hormone.
- More common in women than men
- Can begin suddenly, or it can develop slowly over years
- Most common cause of hypothyroidism in the United States



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HASHIMOTO'S HYPOTHYROIDISM

- Clinical presentation:
  - Low energy, depression, cold intolerance, thinning hair, dry skin, rash, mild weight gain, constipation
  - May be asymptomatic or present only with growth/pubertal delay or menstrual irregularities
  - +/- Goiter
- Confirmatory testing:
  - TSH and Free T4
    - Could have normal labs or high TSH with low Free T4
  - Thyroid peroxidase antibody (TPO) and/or antithyroglobulin (Anti-TG) antibodies
    - One or both will be positive
- Treatment:
  - May include observation in cases of subclinical disease with TSH <10 mIU/mL
  - In cases with overt hypothyroidism and TSH >10 mIU/mL, thyroid hormone replacement with levothyroxine is the standard of care
    - Typical full replacement doses by age:
      - Infants: 10-15mcg/kg/d
      - Toddlers and preschoolers: 6-10mcg/kg/d
      - Pre-pubertal to early pubertal children: 2-4mcg/kg/d
      - Adults 1.5-2mcg/kg/d
- Follow-up:
  - Serum TSH and Free T4 every 6-12 months

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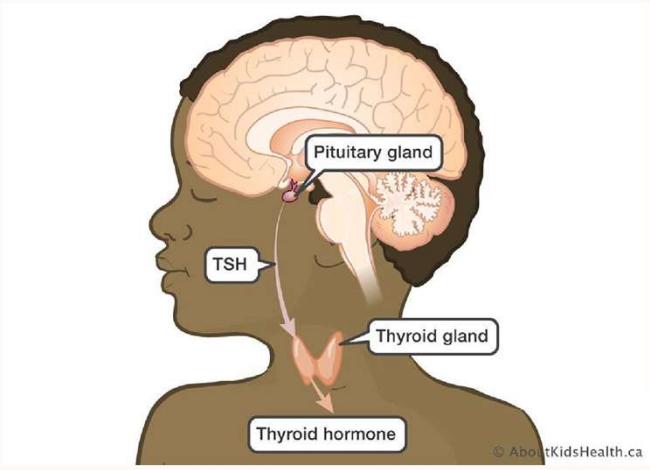
CENTRAL HYPOTHYROIDISM

- The pituitary, the "master gland," tells the thyroid how much hormone to make. When the pituitary is damaged by a tumor, radiation, or surgery, it may no longer be able to give the thyroid instructions, and the thyroid may stop making enough hormone.
- Prevalence is much lower than primary hypothyroidism
- Pituitary mass lesions, especially pituitary adenomas, are the most common cause



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CENTRAL HYPOTHYROIDISM

- Clinical presentation:
  - Similar to primary hypothyroidism but usually more mild
  - Can include fatigue, cold intolerance, muscle cramps, headache, and weight gain
  - Goiter is not a typical finding
- Confirmatory testing:
  - Low or low-normal Free T4 with low, normal, or slightly elevated TSH (<10)
- Treatment:
  - Levothyroxine is the treatment of choice
  - Weight-based dosing of 1.6mcg/kg/d
  - Dose should be adjusted according to the patient's symptoms and serum free T4 values, aiming to maintain the serum free T4 concentration in the upper part of the normal range
- Follow-up:
  - Dose of levothyroxine will be adjusted according to patient's symptoms and serum Free T4 values
  - Serum TSH cannot be used to monitor therapy

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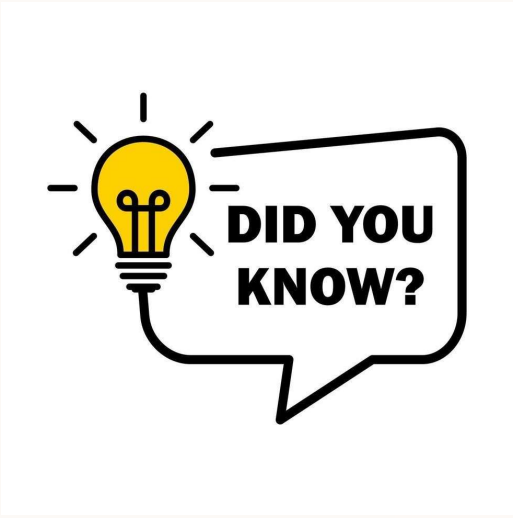
CENTRAL HYPOTHYROIDISM

- Pituitary-adrenal function should be assessed, usually by a corticotropin (ACTH) stimulation test, **BEFORE levothyroxine therapy is started** in ALL patients with central hypothyroidism.
- If adrenal insufficiency is present, glucocorticoid therapy should be given concomitantly with T4
- If left untreated, a life-threatening adrenal crisis could happen!!!



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POST-SURGICAL HYPOTHYROIDISM

- Some people with *thyroid nodules*, *thyroid cancer*, or *Graves' disease* need to have part or all of their thyroid removed. If the whole thyroid is removed, people will become hypothyroid. If part of the gland is left, it may be able to make enough thyroid hormone to keep blood levels normal

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GRAVES DISEASE

- Graves' disease is the most common cause of hyperthyroidism.
- It is an *autoimmune thyroid condition* caused by antibodies that stimulate all the cells in the thyroid gland to make too much thyroid hormone.

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GRAVES DISEASE

- Clinical presentation:
  - Similar to those in adult, however, the onset is subtle and changes may present for months or years before diagnosis is made
  - Common symptoms:
    - ✓ Tachycardia
    - ✓ Failure to gain weight /weight loss,
    - ✓ Decreased appetite, abdominal pain, diarrhea
    - ✓ "Stare" and lid lag (proptosis)
    - ✓ Tremors
    - ✓ Increased anxiety, hyperactivity
    - ✓ DIFFUSE GOITER

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GRAVES DISEASE

Confirmatory testing:

- Elevated Free T4 and Total T3 with suppressed TSH
- Positive Thyroid-stimulating immunoglobulin (TSI)
  - Confirms the presence of a stimulating antibody
  - Can also have positive TPO ab

- Treatment:
  - Antithyroid drug, radioactive iodine (RAI), or thyroidectomy
  - Choice of therapy is determined by induvial consideration of risks and benefits
  - Beta blocker- Helps with tremors, palpitations, tachycardia, and HTN until the thyroid hormone levels have normalized
- Follow-up:
  - Monthly Free T4 and TSH, initially (goal is to have normal Free T4 within the first 3 months after diagnosis)
  - TSH and Free T4 every 6 months until growth and puberty are complete
  - Once puberty is complete, TSH and Free T4 can be monitored annually
  - Regardless of the choice of treatment, all patients with Graves disease will require lifelong follow-up

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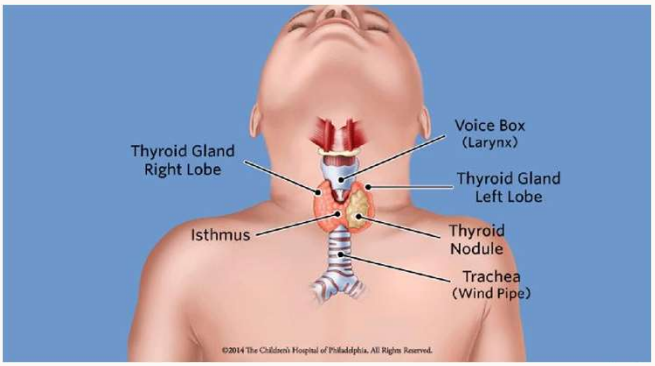
THYROID NODULES

- Less common in children as compared to adults
  - Occurrence is 1-1.5% among children and 13% among adolescences, as compared to up to 65% in adults depending on age
- Though less common, pediatric thyroid nodules have a greater risk of malignancy
  - Risk of malignancy in pediatric thyroid nodules is 22-26%, compared to 5% in adults



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THYROID NODULES

- Cause of pediatric thyroid nodules is largely (90%) unknown.
- Risk factors include radiation exposure, autoimmune thyroiditis, and iodine deficiency (less common in US)
- Clinical presentation:
  - Asymptomatic
  - Most are found during routine physical exams, imaging done for unrelated reasons, or noticed by the patient, a friend, or a parent

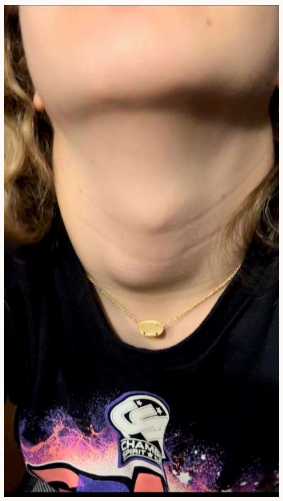

Photo courtesy of Dr. Pallavi Iyer

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THYROID NODULES

- Confirmatory testing:
  - TSH and Free T4
  - Thyroid ultrasound
    - Best tool to diagnose nodule and estimate risk of cancer
  - Radioactive iodine uptake scan to assess for "hot nodule"
  - Fine needle aspiration (FNA) to confirm diagnosis

- Treatment:
  - If cancerous ➡ thyroid surgery
  - If benign ➡ follow-up ultrasound in 6-12 months to make sure nodule has not grown or changed

- Follow-up:
  - Patients who've had partial or complete thyroidectomy will need thyroid hormone supplementation with levothyroxine and to be monitored for hypocalcemia

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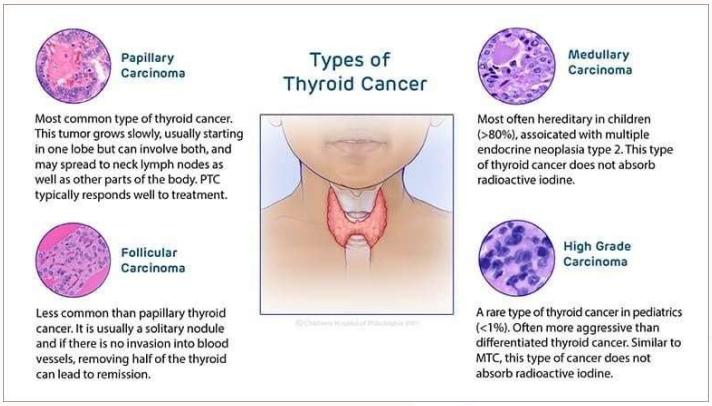
THYROID CANCER

- Pediatric thyroid cancer accounts for 1.5% of all cancers in children younger than 15 years old, and in adolescents 15-19 years of age it accounts for 8% of all cancer
- Papillary thyroid cancer is the most common
- More common in females
- Risk factors: previous exposure to radiation to the thyroid gland, genetic predisposition conditions, and autoimmune thyroiditis



Children's Hospital of Philadelphia

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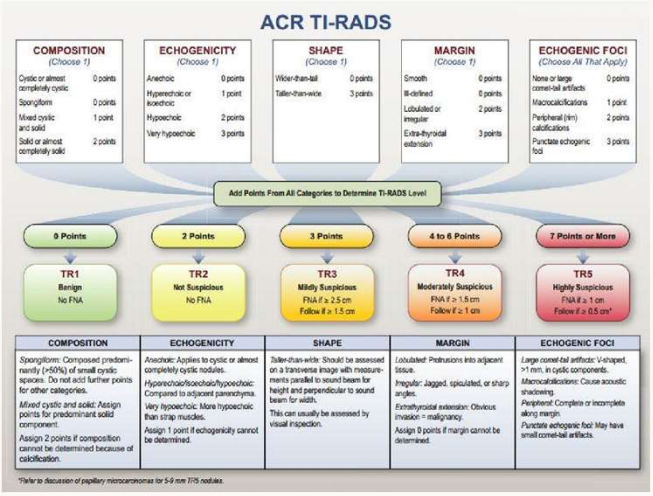
THYROID CANCER

- Confirmatory testing:
  - TSH and Free T4
  - Thyroid ultrasound
    - Learn about size, number, appearance and location of thyroid nodules
    - ACR TI-RADS
  - Radioactive iodine uptake scan to assess for "hot nodule"
  - Fine needle aspiration (FNA) to confirm diagnosis



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THYROID CANCER

- Treatment:
  - Thyroid surgery
    - Either lobectomy or total thyroidectomy
  - Radioactive iodine treatment
    - Destroy remaining thyroid cells after surgery
  - Thyroid hormone replacement therapy
    - Replace thyroid hormone after thyroid-removal surgery
    - May require thyroid hormone suppressive therapy to reduce risk that any remaining cancer cells grow back

- Follow-up:
  - Will require long-term follow-up into adulthood
  - Physical exams, lab tests, and radiological imaging every 3-6 months
  - May become yearly follow-ups if no evidence of persistent or recurrent cancer

- Outlook:
  - Favorable prognosis
  - Vast majority of pediatric patients with thyroid cancer do very well and live long, healthy lives

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THYROID HORMONE TREATMENT

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WHAT IS THE GOAL OF THYROID HORMONE TREATMENT?

1)TO REPLACE INADEQUATE AMOUNTS OF THYROID HORMONE IN HYPOTHYROIDISM

2) TO PREVENT FURTHER GROWTH OF THYROID HORMONE TISSUE WITH SUPPRESSION (THYROID CANCER)

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FORMS OF THYROID HORMONE

- The body makes 2 forms of thyroid hormone: levothyroxine (T4) and tri-iodothyronine (T3).
- T3 is the active hormone that the body uses
- T4 (inactive) is converted to the active hormone T3
- This conversion happens outside of the thyroid gland (e.g. in the liver and brain)
- In general, when thyroid hormone is needed just T4 is prescribed

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LEVOTHYROXINE

- Synthetic version of the body's natural thyroid hormone (*Thyroxine or T4*)
- Many Brand names available: Ermeza; Euthyrox; Levoxyl; Synthroid; Thyquidity; Tirosint; Tirosint-SOL; Unithroid
- FDA Approved Indications:
  - Hypothyroidism
  - Pituitary TSH Suppression
- Drug of choice for hypothyroidism
  - ✓ Safe and effective
  - ✓ Generally well tolerated
- Adverse effects:
  - Usually results from incorrect dosing (too much) and present with a hyperthyroid-like picture OR allergic reaction to one of the preservatives/fillers/coloring agents
- Contraindications:
  - Uncorrected adrenal insufficiency
  - Allergy to drug's active ingredients

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LEVOTHYROXINE

- Dosage forms:
  - Oral tablets
  - Oral capsules
  - Oral solutions
  - Parenteral
- Strengths: Product specific
- Once-daily dosing
- Pregnancy Category A

- Onset of action:
  - Oral: 3 to 5 days; peak therapeutic effect may require 4 to 6 weeks
  - IV: Within 6 to 8 hours
- **Half-life =**
  - **Euthyroid: 6 to 7 days**
  - **Hypothyroid: 9 to 10 days**
  - **Hyperthyroid: 3 to 4 days**

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LEVOTHYROXINE TABLETS

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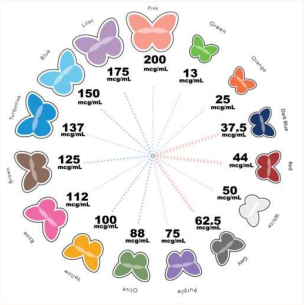
LEVOTHYROXINE LIQUID



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LEVOTHYROXINE CAPSULE

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LEVOTHYROXINE TABLET VS LIQUID/CAPSULE

Tablets	Pros: Cheap, readily available, able to create unique dosing schedules, color-coded	Cons: Can be difficult for families to split tablets, crush and administer to babies
Liquid/capsule	Pros: Easy to administer, doesn't require crushing/mixing, more dosing options available, color coded, contains fewer ingredients	Cons: Not always covered by insurance, can be expensive, not always in stock at pharmacies

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GENERIC VS BRAND NAME

- Both are FDA-approved and regulated
- Both contain the same active ingredient, however, the inactive ingredients differ
- Generic medications are generally favored by insurance companies and less expensive
- Both should work equally well to replace thyroid hormone; however, each person's absorption is different with different inactive ingredients therefore one may be preferred

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Original Investigation | Diabetes and Endocrinology

Comparative Effectiveness of Generic vs Brand-Name Levothyroxine in Achieving Normal Thyrotropin Levels

Juan P. Brito, MD, MSc; Joseph S. Ross, MD, MHS; Lindsey Sangaralingham, MPH; Sarah K. Dutcher, PhD; David J. Graham, MD, MPH; Zhong Wang, PhD; Yute Wu, PhD; Xiaoxi Yao, PhD; Robert C. Smallridge, MD; Victor Bernet, MD; Nilay D. Shah, PhD; Kasia J. Lipska, MD, MHS

Abstract

IMPORTANCE Whether the use of generic vs brand levothyroxine affects thyrotropin levels remains unclear.

OBJECTIVE To compare the effectiveness of generic vs brand levothyroxine in achieving and maintaining normal thyrotropin levels among new users.

DESIGN, SETTING, AND PARTICIPANTS This retrospective, 1:1 propensity score–matched longitudinal cohort study used the OptumLabs Data Warehouse administrative claims database linked to laboratory results from commercially insured and Medicare Advantage enrollees throughout the United States. Eligible patients were adults (aged ≥18 years) with thyrotropin levels ranging from 4.5 to 19.9 mIU/L who initiated use of generic or brand-name levothyroxine from January 1, 2008, to October 1, 2017. Data were analyzed from August 13, 2018, to October 25, 2019.

EXPOSURE Patients received generic or brand-name levothyroxine.

Key Points

Question What is the comparative effectiveness of generic vs brand-name levothyroxine in achieving normal thyrotropin levels?

Findings In a cohort study of 17 598 patients from a national administrative claims database, a similar proportion of generic vs brand-name levothyroxine users achieved target thyrotropin levels.

Meaning These findings suggest that initiation of generic or brand levothyroxine for mild thyroid dysfunction is associated with similar rates of achieving target laboratory outcomes.

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ORIGINAL ARTICLE

Endocrine Care

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Generic Levothyroxine Compared With Synthroid in Young Children With Congenital Hypothyroidism

Jefferson P. Lomenick, Lulu Wang, Steve B. Ampah, Benjamin R. Saville, and Fayrisa I. Greenwald

Department of Pediatrics, Division of Endocrinology (J.P.L.), and Department of Biostatistics (S.B.A., B.R.S.), Vanderbilt University School of Medicine (L.W., F.I.G.), Nashville, Tennessee 37232-9170

Context: Clinicians who prescribe levothyroxine (LT4) for hypothyroidism often feel strongly about using a brand-name drug instead of a generic.

Objective: The objective of the study was to determine whether Synthroid resulted in better control of congenital hypothyroidism than generic LT4.

Design: This was a 5-year retrospective study.

Setting: The study was conducted at 1 tertiary care center.

Patients: Children who were 0–36 months old with congenital hypothyroidism followed up at our center from 2006 to 2011 were treated with either Synthroid exclusively (35 subjects) or generic LT4 exclusively (27 subjects).

Interventions: We recorded the subjects' TSH and free T_4 measurements, how often their LT4 dose was adjusted, and the duration of follow-up.

Main Outcome Measure: TSH variance between the groups was measured. Secondary end points were the frequency of LT4 dose changes and the variance in free T_4.

Results: Using the Wilcoxon rank sum test, there was no difference in TSH SD in the Synthroid group compared with the generic group (median 3.0 vs 2.2, $P = .27$). Using a linear mixed model, children treated with the generic LT4 had lower TSH estimated SD [1.35 with 95% confidence interval (CI) (1.194, 1.526)] than the Synthroid group [1.66 with 95% CI (1.536, 1.803)]. Similarly, no difference was observed in free T_4 SD between the groups using the Wilcoxon rank sum test (median 0.29 generic vs 0.36 Synthroid, $P = .11$), but the generic group had lower free T_4 estimated SD than the Synthroid group using the linear mixed model [0.216 with 95% CI (0.187, 0.249) vs 0.298 with 95% CI (0.273,0.326)]. Frequency of LT4 dosing adjustments was similar between the groups, both in total (median 2.0 for generic vs 3.0 for Synthroid, $P = .097$) and when adjusted for number of TSH checks (ratio 0.25 generic vs 0.31 Synthroid, $P = .45$).

Conclusions: In our study of congenital hypothyroidism, generic LT4 treatment resulted in similar or better control of hypothyroidism compared with Synthroid, as assessed by the clinical outcomes of TSH variance and the frequency of LT4 dosing adjustments. (*J Clin Endocrinol Metab* 98: 653–658, 2013)

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ORIGINAL ARTICLE

Endocrine Care

Generic and Brand-Name L-Thyroxine Are Not Bioequivalent for Children With Severe Congenital Hypothyroidism

Jeremi M. Carswell, Joshua H. Gordon, Erica Popovsky, Andrea Hale, and Rosalind S. Brown

Division of Endocrinology, Boston Children's Hospital and Department of Pediatrics, Harvard Medical School, Boston, Massachusetts 02115

Context: In the United States, generic substitution of levothyroxine (L-T_4) by pharmacists is permitted if the formulations are deemed to be bioequivalent by the Federal Drug Administration, but there is widespread concern that the pharmacokinetic standard used is too insensitive.

Objective: We aimed to evaluate the bioequivalence of a brand-name L-T_4 (Synthroid) and an AB-rated generic formulation (Sandoz, Princeton, NJ) in children with severe hypothyroidism.

Design: This was a prospective randomized crossover study in which patients received 8 weeks of one L-T_4 formulation followed by 8 weeks of the other.

Setting: The setting was an academic medical center.

Patients: Of 31 children with an initial serum TSH concentration >100 mU/L, 20 had congenital hypothyroidism (CH), and 11 had autoimmune thyroiditis.

Main Outcome Measures: The primary endpoint was the serum TSH concentration. Secondary endpoints were the free T_4 and total T_3 concentrations.

Results: The serum TSH concentration was significantly lower after 8 weeks of Synthroid than after generic drug ($P = .002$), but thyroid hormone levels did not differ significantly. Subgroup analysis revealed that the difference in TSH was restricted to patients with CH ($P = .0005$). Patients with CH required a higher L-T_4 dose ($P < .0004$) and were younger ($P = .003$) but were not resistant to thyroid hormone; 15 of 16 CH patients had severe thyroid dysgenesis or agenesis on imaging. The response to generic vs brand-name preparation remained significant when adjusted for age.

Conclusions: Synthroid and an AB-rated generic L-T_4 are not bioequivalent for patients with severe hypothyroidism due to CH, probably because of diminished thyroid reserve. It would therefore

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WHAT ABOUT "NATURAL" THYROID HORMONE?

- Made from dried ground thyroid glands from pigs
- Not FDA-approved but can still be prescribed
- Contain both T4 and T3
- Proportions of T4 and T3 can vary in every batch, which makes it difficult to control blood levels
- Pills still contain binders to hold the pill together, so they are not completely "natural"
- There is no evidence that dessicated thyroid hormone has any advantage over synthetic T4.

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MONITORING AND DOSE ADJUSTMENT

- Adjust dose based on patient's symptoms and TSH and Free T4 levels
- Monitor closely for under/over treatment
  - Undertreatment may decrease intellectual development and linear growth and lead to poor school performance
  - Overtreatment may adversely affect brain maturation and accelerate bone age
- Assess growth and development at every visit

- Serum lab monitoring (TSH and Free T4):
  - 2 and 4 weeks after starting treatment
  - Every 1-2 months during the first year of life
  - Every 2-3 months between ages 1-3
  - Every 3-12 months until growth is complete
  - Every 4-6 weeks after making a dose adjustment

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PROPER ADMINISTRATION OF THYROID HORMONE

- For babies and small children who cannot swallow or chew the pill, parents should crush up each day's tablet and mix it with about a teaspoon of liquid (e.g. water, breast milk, or formula).
- The mixture should be given in small amounts to the baby or small child on a spoon, or from a medicine dropper or syringe.
- Crushed powder can also be administered directly in the baby's cheek
- Do NOT give with large amounts of liquid or food to ensure that baby gets the entire dose of medication

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PROPER ADMINISTRATION OF THYROID HORMONE

- Older children and adolescents should swallow or chew the tablet.
- Levothyroxine is tasteless and is generally very easy for children to chew.
- Prefer that medication be given at the same time of day every day
- Does not necessarily have to be given on an empty stomach; however, absorption may be affected by food so it should be taken consistently with or without food.
- Foods/medications that may prevent the medication from being fully absorbed:
  - Soy formulas or soy milk
  - Iron supplements
  - Calcum supplements
  - Antacids

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ANTITHYROID MEDICATION

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THIONAMIDES

- Anti-thyroid medications
- Found in 1943 to inhibit new thyroid hormone synthesis
- Methimazole, carbimazole, and propylthioracil (PTU) are effective treatments in Graves hyperthyroidism
- **Methimazole** and **PTU** are the only thionamides available in the US

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METHIMAZOLE

- Brand name: Tapazole
- Preferred choice of antithyroid medication over PTU, *except during the first trimester of pregnancy*
- Advantages:
  - ✓ Faster achievement of euthyroidism
  - ✓ Once-daily dosing and better compliance
  - ✓ Little or no effect on subsequent effect of radioiodine therapy
  - ✓ Less hepatotoxicity

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METHIMAZOLE

- Dosage form: Oral tablets
- Strengths: 5mg and 10mg

- Dosing varies according to severity:
  - Mild hyperthyroidism:
    - Small goiter
    - Free T4 1-1.5x upper normal limit
    - Start with 5-10mg once daily
  - Moderate hyperthyroidism
    - Goiter
    - Free T4 1.5-2x upper normal limit
    - Start with 10-20mg once daily
  - Severe hyperthyroidism
    - Large goiter
    - Free T4 2-3x upper normal limit
    - Start with 20-40mg once daily

We initially administer in divided doses (BID or TID) to normalize thyroid function more quickly, then change to once daily dosing if tolerated and as dose is reduced

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METHIMAZOLE

- Side effects:
  - Common: pruritus, rash, urticaria, arthralgias, arthritis, fever, abnormal taste sensation, nausea, or vomiting
  - Rare but serious: agranulocytosis, hepatoxicity, pancreatitis
- Contraindications: Hypersensitivity to methimazole or any component of the formulation.
- Pregnancy Category D
  - Avoid specifically during 1st trimester
- Onset of action = 12-18 hours
- Half-life = 4-6 hours

- FDA-Approved Indications:
  - Patients with Graves disease
  - Patients with toxic multinodular goiters who are not a good candidate for surgery or radioactive iodine therapy
  - To alleviate symptoms before undergoing thyroidectomy or radioactive iodine therapy
- Off-Label Use:
  - Used to treat thyrotoxicosis or thyroid storm

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METHIMAZOLE

- Monitoring:
  - Graves hyperthyroidism:
    - TSH, Free T4, Total T3 initially at every 4-6 week intervals until stable
    - Once the Free T4 and T3 are within normal range, can decrease dose of methimazole by 30-50%
    - TSH, Free T4, Total T3 every 6 months once a stable dose is achieved
    - CBC, liver function tests
      - ALWAYS check CBC with fever illness or pharyngitis and LFT with signs/symptoms of hepatitis
- Duration of therapy:
  - In preparation for radioiodine therapy:
    - ✓ Pretreat for 4-6 weeks until thyroid function normalizes
    - ✓ Stop 3 days before and restart 3 days after to allow better control of thyroid function post-radioiodine administration
  - In preparation for thyroidectomy:
    - ✓ Pretreat for 4-6 weeks until thyroid function normalizes
    - ✓ Stop on the day of surgery
  - Primary therapy:
    - ✓ Initially treat for 12-18 months
    - ✓ If remission is not obtained after a 12- to 18-month course, long-term treatment with methimazole for 10 years or more has been shown to be effective and safe

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PROPYLTHIORACIL (PTU)

- **BLACK BOX WARNING= HEPATOXICITY**
  - **NOT RECOMMENDED FOR USE IN PEDIATRIC PATIENTS**
  - **Reserve PTU for patients who cannot tolerate methimazole and in whom radioactive iodine therapy or surgery are not appropriate treatments for the management of hyperthyroidism**
- Preferred choice of drug in:
  - 1st trimester of pregnancy
  - Thyroid storm
- Dosage form and strength: Oral tablet, 50mg
- Dosing:
  - 6-10 years: 50-150mg/day divided every 8 hours
  - >10 years: 150-300 mg/day divided every 8 hours
  - Maintenance dose (once euthyroid): 50mg twice daily

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PROPYLTHIORACIL (PTU)

- Side effects:
  - Common: pruritus, rash, urticaria, arthralgias, arthritis, fever, abnormal taste sensation, nausea, or vomiting
  - Rare but serious: agranulocytosis, hepatoxicity, pancreatitis
- Contraindications: Hypersensitivity to propylthiouracil or any component of the formulation
- Pregnancy Category D
- Onset of action = 24-36 hours
- Half-life = ~1 hour
- FDA-Approved Indications:
  - Treatment of hyperthyroidism in patients who are intolerant of methimazole and for whom surgery or radioactive iodine therapy is not an appropriate treatment regimen
  - Treatment of of hyperthyroid symptoms in preparation for thyroidectomy or radioactive iodine therapy (in patients who are intolerant of methimazole).
- Off-Label Use:
  - In thyroid storm and thyrotoxicosis crisis

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PROPYLTHIORACIL (PTU)

- Monitoring:
  - Signs and symptoms of illness (ie fever, sore throat, skin eruptions, general malaise) or vasculitis.
  - CBC with differential (baseline and if development of febrile illness or pharyngitis occurs)
  - Prothrombin time (especially before surgical procedures)
  - LFTs (bilirubin, alkaline phosphatase, ALT, AST at baseline and if symptoms of liver injury occur)
  - Serum free T_4 and total T_3 at 4- to 6-week intervals during dose titration, then every 2 to 3 months once euthyroid levels are achieved
  - Thyroid stimulating hormone (TSH) periodically throughout treatment; TSH is not an adequate parameter to assess initial response as levels may remain suppressed for several months after starting therapy

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RADIOACTIVE IODINE THERAPY

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RADIOACTIVE IODINE (RAI)

- Two radioactive forms commonly used:
  - I-123 (does not damage thyroid cells)
  - I-131 (can be used to destroy thyroid cells)
- Both are given as a pill or liquid that you swallow
- Both are safe to use even if you have had an allergic reaction to seafood or CT contrast

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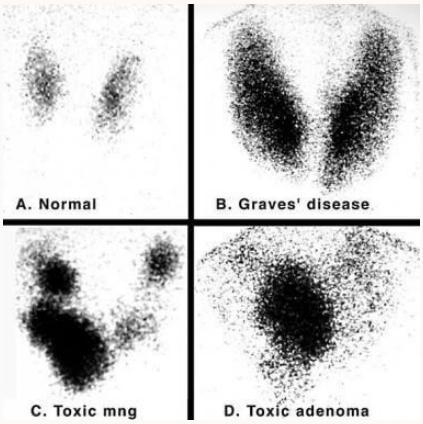
RAI FOR THYROID IMAGING

- I-123 is used to diagnose thyroid problems since it does not damage cells
- I-123 can be used to perform a thyroid uptake and/or scan
- Thyroid uptake and scan measures the thyroid's function
- Patients take the 1-123 and then wait for the iodine to collect in the thyroid
- 1st scan is done at 4 hours
- 2nd scan is done at 24 hours
- No special radiation precautions are necessary after taking 1-123



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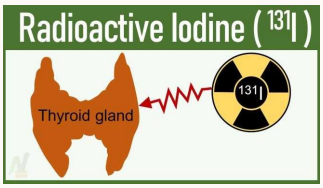
RAI FOR TREATMENT

1-131 is used to treat an overactive thyroid gland (hyperthyroidism) or thyroid cancer

- ❑ Hyperthyroidism:
  - Low dose of I-131 is given to destroy over-active thyroid disease
  - Can be used for either Graves or toxic (hot) thyroid nodule
  - Patients will have to follow radiation precautions
  - RAI treatment may take several months to have full effect
  - Patients will become hypothyroid after treatment and will need to supplement with thyroid hormone



- ❑ Thyroid cancer:
  - Larger doses of I-131 are used to destroy thyroid cancer cells remaining after thyroid cancer surgery
  - Patients may be asked to follow a low iodine diet prior to treatment
  - This treatment is only effective when TSH level is high
    - To increase TSH levels, patients will stop their thyroid hormone pills
  - Patients will be asked to follow radiation precautions

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THYROID SURGERY

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THYROID SURGERY

- Graves disease
  - Surgery (near-total or total thyroidectomy) is an effective form of therapy for Graves disease
  - Usually used as a secondary treatment option when anti-thyroid drug therapy fails or causes side effects
  - Surgery is preferred in children <5yo when definitive therapy is needed because RAI is not recommended in this age group

Preparation:
- Patient should continue methimazole therapy until T4 levels normalize
- x1 week prior to surgery, iodine drops are started to inhibit thyroid hormone production; this makes the gland more firm and less vascular

Post-operatively:
- Hypothyroidism is nearly universal in children who undergo total thyroidectomy, and levothyroxine is started on first post-op day
- Younger pediatric patients are at higher risk for transient hypoparathyroidism and may be treated with high-dose vitamin D or calcitriol x1 week prior to surgery

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THYROID SURGERY

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- Thyroid nodules:
  - Surgical removal of nodules is usually recommended if nodule is very large (>3cm across) or if producing too much thyroid hormone ("hot nodule") or if nodule is impacting quality of life
- Thyroid cancer:
  - Total or near-total thyroidectomy is the recommended surgical procedure for PTC and MTC
  - Lobectomy is preferred initially for FTC

Preparation:

- Specific instructions on when to stop eating, drinking, and taking medications will be given prior to surgery

Post-operatively:

- Levothyroxine is given post-operatively to replace thyroid hormone and suppress thyroid cell growth by suppressing TSH
- PTH is checked in the recovery room to predict temporary hypocalcemia, if low then calcium carbonate (TUMs) with or without calcitriol is started
- Calcium, PTH, TSH are re-checked 2 weeks after surgery

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THYROID SURGERY

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- Patients may experience a sore throat from placement of the endotracheal tube
- Ibuprofen and/or acetaminophen are usually sufficient for pain control
- There are no stitches to remove, usually one subcutaneous stitch and then incision is covered with surgical glue
- Very few activity restrictions, allowing them to return to school within days postoperatively

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REFERENCES:

- *Thyroid Hormone Treatment in Children and Adolescents*. (n.d.). American Thyroid Association. https://www.thyroid.org/thyroid-hormone-treatment-children-adolescents/
- *Thyroid nodules in children and adolescents*. American Thyroid Association. (n.d.). https://www.thyroid.org/thyroid-nodules-children-adolescents/
- Congenital Hypothyroidism. (n.d.). Www.endocrine.org. https://www.endocrine.org/patient-engagement/endocrine-library/congenital-hypothyroidism
- The Children's Hospital of Philadelphia. (2023, January 18). *Thyroid cancer in children*. Children's Hospital of Philadelphia. https://www.chop.edu/conditions-diseases/thyroid-cancer-children
- Iyer, P.& Chen, H. (2021). *Thyroid and Parathyroid Disorders in Children: A Practical Handbook*. CRC Press.
- Eghtedari B, Correa R. Levothyroxine. [Updated 2023 Aug 28]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2024 Jan-. Available from: https://www.ncbi.nlm.nih.gov/books/NBK539808/
- Levothyroxine: Drug information. In: UpToDate, Connor RF (Ed), Wolters Kluwer. (Accessed on February 29, 2024).
- Brito JP, Ross JS, Sangaralingham L, et al. Comparative Effectiveness of Generic vs Brand-Name Levothyroxine in Achieving Normal Thyrotropin Levels. JAMA Netw Open. 2020;3(9):e2017645. doi:10.1001/jamanetworkopen.2020.17645
- Commissioner, O. (n.d.). Older therapies aren't always better for thyroid hormone replacement. U.S. Food and Drug Administration. https://www.fda.gov/consumers/consumer-updates/older-therapies-arent-necessarily-better-thyroid-hormone-replacement Ross Douglas.
- Propylthiouracil: Drug information. In: UpToDate, Connor RF (Ed), Wolters Kluwer. (Accessed on March 1, 2024).

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60

REFERENCES:

- Central hypothyroidism. In: UpToDate, Connor RF (Ed), Wolters Kluwer. (Accessed on February 22, 2024).
- Clinical manifestations and diagnosis of Graves disease in children and adolescents. In: UpToDate, Connor RF (Ed), Wolters Kluwer. (Accessed on February 23, 2024).
- Treatment and prognosis of Graves disease in children and adolescents. In: UpToDate, Connor RF (Ed), Wolters Kluwer. (Accessed on February 23, 2024).
- Thionamides in the treatment of Graves' disease. In: UpToDate, Connor RF (Ed), Wolters Kluwer. (Accessed on February 23, 2024).
- Thionamides: Side effects and toxicities. In: UpToDate, Connor RF (Ed), Wolters Kluwer. (Accessed on February 23, 2024).
- Awosika AO, Singh G, Correa R. Methimazole. [Updated 2023 Sep 13]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2024 Jan-. Available from: https://www.ncbi.nlm.nih.gov/books/NBK545223/
- *Brand and generic medication explained*. American Thyroid Association. (n.d.-a). https://www.thyroid.org/brand-generic-medication/
- Carswell JM, Gordon JH, Popovsky E, Hale A, Brown RS. Generic and brand-name L-thyroxine are not bioequivalent for children with severe congenital hypothyroidism. J Clin Endocrinol Metab. 2013 Feb;98(2):610-7. doi: 10.1210/jc.2012-3125. Epub 2012 Dec 21. PMID: 23264396; PMCID: PMC3565118.
- Lomenick JP, Wang L, Ampah SB, Saville BR, Greenwald FI. Generic levothyroxine compared with synthroid in young children with congenital hypothyroidism. J Clin Endocrinol Metab. 2013 Feb;98(2):653-8. doi: 10.1210/jc.2012-3558. Epub 2013 Jan 4. PMID: 23293325.
- *Radioactive Iodine*. American Thyroid Association. (n.d.). https://www.thyroid.org/radioactive-iodine/

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