Drugs used in hyperthyroidism & hypothyroidism

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- Main text
- Male slide
- Female slide
- Important
- Dr, notes
- Extra info

EDITING FILE

Objectives

- Describe different classes of drugs used in hyperthyroidism and their mechanism of action
- Recognize treatment of special cases such as hyperthyroidism during pregnancy, Graves' disease and thyroid storm
- Understand their pharmacological effects, clinical uses and adverse effects
- Describe different classes of drugs used in hypothyroidism and their mechanism of action
- Understand their pharmacological effects, clinical uses and adverse effects
- Recognize treatment of special cases of hypothyroidism such as myxedema coma

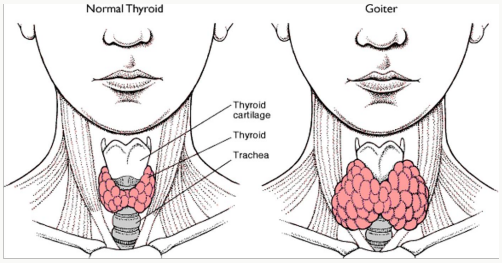
Dr. Fouda Video

For more quizzes & mnemonics check our channel :) !

Thyroid Gland

Thyroid Function

1. **Thyroid hormones:** unique biological molecules in that they incorporate **iodine** in their structure.
2. Growth & development, especially embryo & brain.
3. **Thermoregulation:** ↑ basal metabolic rate (BMR).
4. Helps maintain metabolic energy balance.
5. **CVS**: ↑ HR & cardiac output → ↑ oxygen demand.



Normal amount of thyroid hormones are essential for **normal growth and development** by maintaining the level of energy **metabolism** in the tissue.

Either too little or too much thyroid hormones → disorders to the body.

Iodine

Iodine

1. Adequate iodine intake (diet - water) is required for normal thyroid hormone production.
2. **Sources:** iodized salt - iodized bread - dairy products - shellfish. *Inactive "iodide"*
3. **Minimum requirement:** 75 micrograms/day.

Iodine Metabolism

1. Dietary iodine absorbed in GIT

2.A. Taken Up by the Thyroid Gland
"***Oxidized*** *by peroxidase in follicle lumen*"

I^- *Iodide* —**Peroxidase**→ I_2 *Iodine*

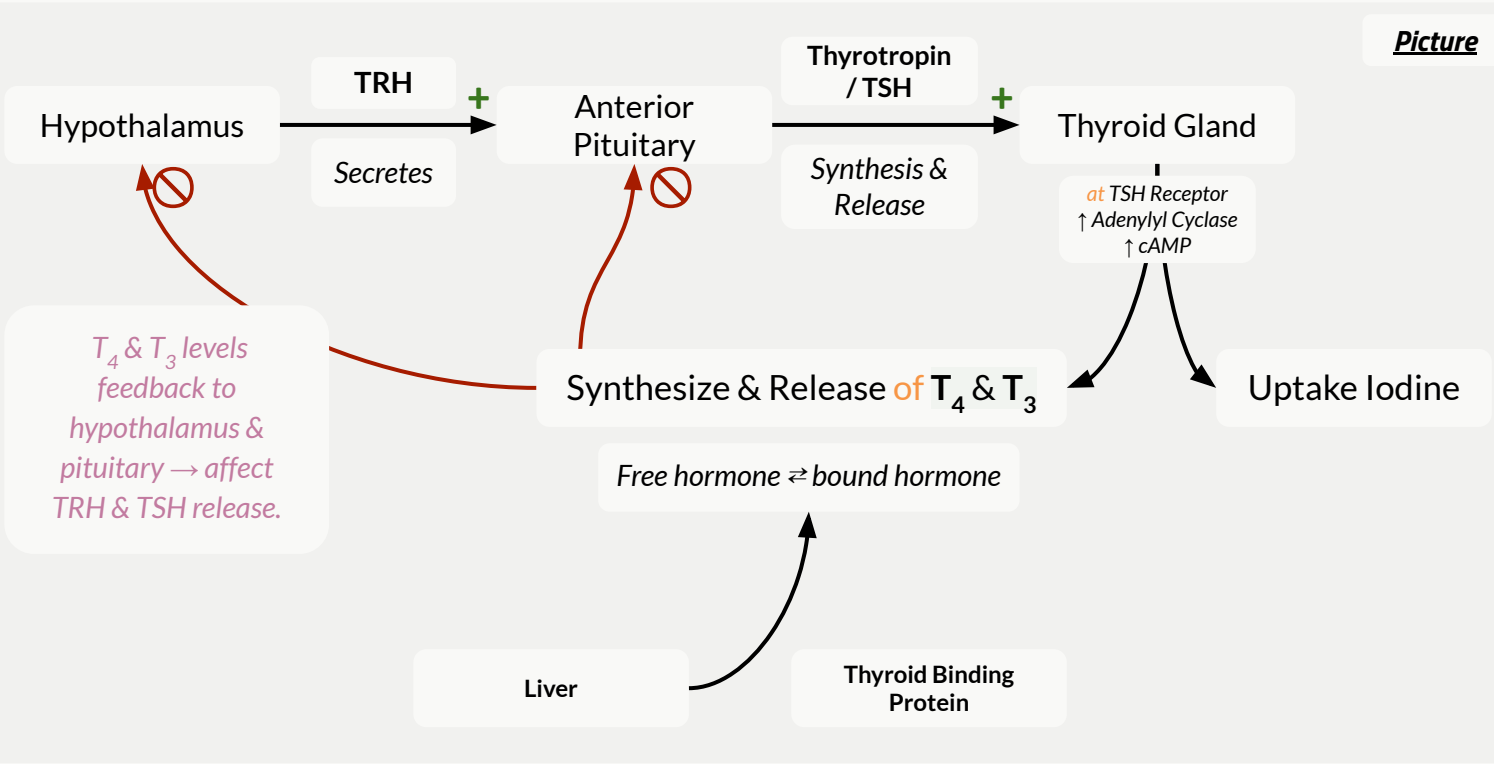
Oxidized iodine is used in **thyroid hormones** production.

2.B. Removed from Body by Kidneys

-

Thyroid Regulation

Picture



Thyroid Hormone Synthesis

Picture

Iodide trapping: uptake of iodide by the thyroid gland.

Oxidation of iodide to its active form by thyroid **peroxidase** (*key enzyme of synthesis*).

Dr. Anfal: Thyroid hormones = 2 Tyrosine + 3 or 4 Iodine.

Iodine organification: iodination of **tyrosyl** groups of **thyroglobulin** → MIT + DIT.

Formation of **T_4 and T_3** (*biologically active thyroid hormones*) from MIT and DIT: thyroid **peroxidase** (TPO).

Thyroid Regulation

TSH release is influenced by: hypothalamic **TRH** + **thyroid** hormones.

Thyroid hormones exert negative feedback on TSH release at the level of anterior pituitary:

- Inhibition of **TSH synthesis.**
- Decrease in **pituitary receptors for TRH.**

TRH: Thyrotropin-Releasing Hormone.
TSH: Thyroid Stimulating Hormone or Thyrotropin.

T_3: Triiodothyronine.
T_4: Tetraiodothyronine or thyroxine.

MIT: MonoIodoTyrosine.
DIT: DiIodoTyrosine.

Thyroid Hormones Disorders

Thyrotoxicosis	- All disorders with **increased** levels of circulating thyroid hormones. - Hypermetabolic state caused by excess thyroid hormone at the tissue level. *-increase thyroid hormones due to any cause-*
Hyperthyroidism	- Disorders in which thyroid gland secretes **increased** amounts of hormones. *-increase thyroid hormones due to hyperfunctioning of thyroid gland-* - Increased thyroid hormones synthesis and secretion.
Hypothyroidism	- Disorders in which thyroid gland secretes **decreased** amounts of **hormones**.
Thyroid Neoplasia	- Benign **enlargement** or **malignancies** of the gland.

1. Thyrotoxicosis

- All patients with hyperthyroidism have **Thyrotoxicosis**.
- **Not** all patients with thyrotoxicosis have hyperthyroidism.

Causes of Thyrotoxicosis

High RAIU
- **Graves' disease (60 - 80%)**
- **Multinodular goitre (14%)**
- **Adenomas / carcinomas**

RAIU: RadioActive Iodine Uptake.

Low RAIU
- **Thyroiditis**
- **Iodine-induced thyrotoxicosis:**
  - **Drugs (e.g. Amiodarone)**
  - **Radiographic contrast media**

Symptoms

- Irritability
- Dysphoria
- Diarrhea
- Heat intolerance & sweating
- Palpitations
- Weight loss
- Fatigue / weakness

Signs

- Arrhythmias
- Pretibial myxedema
- Warm, moist skin
- Thyroid enlargement
- Exophthalmos

Hyperthyroidism: Treatment

Thioamides (*antithyroid drugs*) → **Iodides** → **Radioactive Iodine** → **Adrenoceptor (β) Blockers** → **Surgery (Subtotal Thyroidectomy)** very large gland or multinodular goiter.

1. Thioamides (Antithyroid Drugs)

Drugs	Propylthiouracil (PTU)	Methimazole / Carbimazole *Carbimazole: Prodrug* → converted to methimazole (active metabolite)
M.O.A.	• Inhibit thyroid hormones synthesis by **inhibiting peroxidase** enzyme that catalyzes the **iodination of tyrosine** residues. • **Propylthiouracil (but not Methimazole) Blocks the conversion of T_4 to T_3** in peripheral tissues. *dual action, only Propylthiouracil*	
P.K.	• **Absorption:** rapid. • **Accumulation:** thyroid.	• **Placenta:** crosses placenta
	• **Administration:** every 6 - 8 hrs. • **Plasma half-life:** 1.5 hrs (short). • **Protein binding:** 80 - 90%. • **Excretion:** kidney (inactive metabolite) within 24 hrs.	• **Administration:** every 8 hrs. • **Plasma half-life:** 6 hrs (long). • **Protein binding:** mostly free. • **Excretion:** slow, 60 - 70% is recovered in urine in 48 hrs.
Pregnancy & Breast feeding	• **Pregnancy [Drug of choice]:** highly **protein bound**→ crossing placenta is less readily. • **Breast feeding**: less secreted in breast milk→ recommended.	• **Pregnancy:** not recommended. • **Breast feeding:** secreted → not recommended.
ADRs	• **Skin reactions:** urticarial or macular reactions (4 - 6% frequency) • **Arthralgia** (1 - 5%) • **GIT:** gastric distress + nausea (1 - 5%) • Polyarthritis (antithyroid **arthritis**) (1 - 2%) • **Agranulocytosis:** Graves' disease patients | within 90 days of treatment. (0.1 - 0.5%)	
	• Immunoallergic **hepatitis:** almost exclusive in PTU (0.1 - 0.5%) • ANCA-positive vasculitis (Rare) **ANCA:** AntiNeutrophil Cytoplasmic Antibodies.	**Only Methimazole:** • **Abnormal sense of taste or smell** (Rare)

2. Iodides: (Lugol's Solution | Potassium Iodide)

Drugs	Organic Iodides	Potassium Iodide
Examples	• Iopanoic acid Ipodate	-
M.O.A.	• **Inhibit thyroid hormone synthesis and release.** • Block the peripheral conversion of **T_4 to T_3**. "like PTU" • The effect is **not sustained** (***temporary*** *remission of symptoms*). • **Decreases the blood flow** to the thyroid (↓ Vascularity)	

2-Iodides: (Lugol's Solution | Potassium Iodide) Cont.

Drugs	Organic Iodides	Potassium Iodide
Uses	• **Prior to thyroid surgery:** ↓ ***vascularity*** & ***size*** *of gland*. *"it has a temporary effect"* • Thyrotoxicosis	
Precautions	• Not used as a **single therapy** *"temporary effect"* • Not used in **pregnancy** • **Iodism [*skin rash - hypersalivation - oral ulcers - metallic taste - bad breath*]**: iodine is not much used now → rare. *"may cause iodine toxicity (iodism)"*	

3-Radioactive Iodine (RAI)

Drug	Radioactive Iodine
M.O.A.	• **^{131}I isotope:** therapeutic effect due to emission of β rays. • **Accumulates** in the thyroid gland → **destroys parenchymal cells** →long-term decrease in thyroid hormone levels.
P.K.	• **Administration:** easy, effective, painless, and less expensive - Solution or capsules. • **Clinical improvement:** 2 - 3 months. • **Half-life:** 5 days. • **Pregnancy:** crosses placenta. **#** *in pregnancy* • **Breast feeding:** secreted in breast milk.
Uses	• Hyperthyroidism mainly in **old patients** (above 40). *"Used commonly, but not a first choice"* • **Graves'** disease. • Patients with **toxic nodular goiter**. • **Diagnostic**. *"not only treatment"*
#	• **Pregnancy**
Disadvantages	• **Delayed hypothyroidism** (high incidence). *"Due to severe disruption of thyroid follicles"* • **Cytotoxic** actions: necrosis of follicular cells followed by fibrosis (large doses). • **Genetic** damage. • Leukemia & **neoplasia**.

4- Adrenoceptor Blocking Agents (Beta Blockers)

Drug	Propranolol	Atenolol	Metoprolol
M.O.A.	• Beta Blockers.		
Uses	• **Adjunctive** *symptomatic* **therapy** to **relief adrenergic symptoms** of hyperthyroidism [**tremor** - **palpitation** - heat intolerance - **nervousness** - tachycardia].		
#	• **Asthmatic patients**. *"Because it is nonselective"*	*"Atenolol & Metoprolol **can** be used in asthmatics"*	

Hyperthyroidism: Treatment in Pregnancy

Overview	- Better to start therapy **before pregnancy** with ^{131}I or subtotal **thyroidectomy** to avoid acute exacerbation during pregnancy **- Drug of Choice: Propylthiouracil (PTU)** **- Contraindication: radioiodine (RAI)** Pregnancy→ PTU

Hyperthyroidism

Thyroid Storm

- Sudden acute exacerbation of **all of symptoms of thyrotoxicosis** [life threatening syndrome].
- **Hypermetabolism** & excessive adrenergic activity.
- Death may occur due to **heart failure** & shock.
- Medical emergency!

Dr. Assiri: Not very important, because guidelines usually change with time.

Management

- In an **ICU**: close monitoring of vital signs + access to invasive monitoring & inotropic support.
- Correct **electrolyte** abnormalities.
- Treat cardiac **arrhythmia** (if present).
- Aggressively control **hyperthermia** by applying **ice packs**.
- Promptly administer **antiadrenergic drugs** (*propranolol*) → **minimize sympathomimetic** symptoms.
- High-dose **PTU** (*early onset of action*) → risk of severe liver injury & acute liver failure.
- **Iodine** compounds (Lugol's iodine or potassium iodide) orally / nasogastric tube.
- **Hydrocortisone** 50 mg IV every 6 hours → prevent shock.
- Plasmapheresis (rarely).

Toxic multinodular goiter

Features

- Second most common cause of hyperthyroidism.
- Most cases in women in 5^{th} to 7^{th} decades.
- Often have long standing goiter.
- Symptoms usually develop slowly.

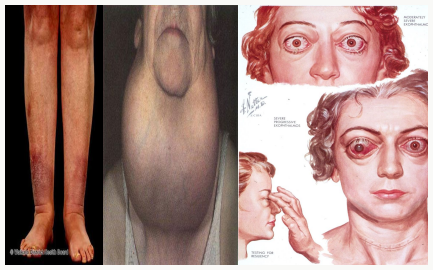
Hyperthyroidism

Diffuse Toxic Goiter (Graves' Disease)

Cause	Epidemiology
Thyroid stimulating immunoglobulins that stimulate TSH receptor → sustained thyroid over activity.	◦ Mainly in young adults aged 20 to 50. ◦ 5 times more frequent in women.

Clinical Presentation

- Swelling and soft tissues of hands and feet.
- Clubbing of fingers and toes.
- Half of cases have **exophthalmos** (not seen with other causes of hyperthyroidism).
- 5% have **pretibial myxedema** (thyroid dermopathy).



Both Drs: Not very important

Management of Hyperthyroidism due to Graves' Disease

Severe	Mild/Moderate
• Markedly elevated serum T_4 or T_3 • Very large goiter > 4x	• Small or moderately enlarged thyroid. • Children • Pregnant/lactating women.
- **Adults:** definitive therapy with radioiodine. - **Elderly + heart disease:** Normalization of thyroid function with antithyroid drugs before surgery. *"Iodides are used before surgery"*	1. Primary antithyroid drug therapy. ◦ Methimazole 5 - 30 mg/day | PTU in pregnancy. 2. **Monitor** thyroid function: every 4 - 6 weeks until **euthyroid state** achieved. 3. **Discontinue** drug: after 12 - 18 months. 4. **Monitor** thyroid function: every 2 months for 6 months, then less frequently. a. **Relapse** → definitive radioiodine (*adults*) | antithyroid 2nd course (*children*). b. **Remission** → monitor thyroid function every 12 months indefinitely.

Hypothyroidism

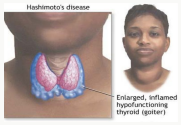
Thyroid gland does not produce enough hormones, may be:

1. Congenital	2. Primary	3. Secondary
(in children): **dwarfism** (delay in growth) + **cretinism** (delay intellectual development).		

Diagnosis	Prevalence
low plasma levels of T_3 & T_4.	most at risk include those over age 50 & mainly in females. 14/1000 females and 1/1000 males.

Primary Hypothyroidism

Inadequate function of the gland itself



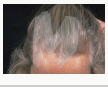
- **Iodine deficiency**: most common cause of *primary hypothyroidism* & *endemic goiter*.
- **Autoimmune**: Hashimoto's thyroiditis.
- Radioactive iodine treatment of hyperthyroidism.
- Post thyroidectomy.
- Antithyroid drugs: CMZ - PTU.
- Drugs: lithium - amiodarone.
- Subacute thyroiditis.
- Thyroid carcinoma.

Secondary Hypothyroidism

- Hypothalamic disease
- Pituitary disease

Early Manifestations of hypothyroidism

- Cold intolerance
- Weakness
- Paleness
- Thin, brittle hair and fingernails
- Constipation
- Muscle/ joint pain
- Fatigue/lack of energy



Late Manifestations of hypothyroidism

- Dry flaky skin
- Hoarseness
- Puffy face, hands, & feet
- Decreased sense of taste and smell
- Menstrual disorder
- Eyebrow thinning

Hypothyroidism & Pregnancy

20-30 % increase in thyroxine is required because:

- **Elevated maternal thyroxine binding globulin** (**TBG**) induced by estrogen.
- Early development of fetal brain which depends on maternal thyroxine.

Hypothyroidism Treatment

Replacement therapy with synthetic thyroid hormone preparations

1. Levothyroxine (T_4)
2. Liothyronine (T_3)
3. Liotrix (T_4 + T_3)

Levothyroxine (T_4) *L-thyroxine/eltroxin*

M.O.A.

★ Synthetic form of **thyroxine** (T_4).

P.K.

- Stable
- **Administration:** once daily. Oral **(0.025 - 0.3 mg tablets)** | Parenteral **(200 - 500 µg)**.
- **Dose: 12.5 – 25 µg/day** for two weeks and then increased every two weeks.
- **Half-life:** 7 days (long) → less daily doses → better for life long therapy.
- **Absorption:** increased when hormone is given on empty stomach.
- **Restore normal levels:** within **2-3 weeks**.

Uses

- **[Drug of choice] for replacement therapy.** Especially in CVD patients instead of Liothyronine
- Hypothyroidism regardless of etiology:
  Congenital - Hashimoto thyroiditis - **Pregnancy**.

ADRs
Overdose
"symptoms of Hyper"

Children:

- Restlessness
- Insomnia
- Accelerated bone maturation

Adults:

- Cardiac arrhythmias (atrial fibrillation)
- Tachycardia
- Tremor / Restlessness
- Change in appetite
- **Weight loss**
- Headache
- Heat intolerance
- Muscle pain

Precautions

- Start with reduced dosage in old patients & patients with cardiac problems. "after taking the drug, symptoms of hyperthyroidism may start"

Liothyronine (T_3)

P.K.

- More **potent** (3-4 times).
- **Rapid onset of action** compared to levothyroxine.
- **Half-life: short** → not recommended for routine replacement therapy (require multiple daily dose)
- **Administration: multiple daily doses. Oral (5 - 50µg tablets)** | Parenteral **(10 µg/ml).**

#

- **Cardiac patients** "any misdosing may cause serious problems (CVS symptoms of hyperthyroidism)"

Drug	Levothyroxine (T_4)	Liothyronine (T_3)
Potency	1 "less potent"	4 "more potent"
$T_{1\backslash 2}$ (days)	6-7 "longer → less daily doses"	⩽2 "shorter → multiple doses"
Protein binding (%)	99.96	99.5

Liotrix

M.O.A.

- Combination of **synthetic T_4 & T_3** in a ratio 4:1 that attempt to mimic the natural hormonal secretion.

limitations

- **High cost**
- Lack of therapeutic rationale because 35% of T_4 is peripherally converted to T_3.

Hypothyroidism Treatment

Thyroid Hormone Metabolism

Major metabolism pathway: sequential deiodination.

80% of circulating T_3 is derived from peripheral T_4 by mono-deiodination

Major site of degradation: liver (for both T_4 and T_3).

80% of daily dose of T_4 is deiodinated → equal amounts of T_3 and rT_3 (inactive).

rT_3: Reverse T_3.

Myxedema Coma

- Life-threatening hypothyroidism
- **Treatment of choice:** loading dose of **Levothyroxine** IV 300 - 400µg initially followed by 50µg daily.
- I.V. liothyronine (rapid response) → may provoke cardiotoxicity.
- Adrenal and pituitary insufficiency → I.V. hydrocortisone.

MCQ

1. Which ONE of the following is the most suitable drug for a pregnant woman with hyperthyroidism?

A. PTU	B. Methimazole	C. Octreotide	D. Carbimazole

2. A patient with multinodular goiter is going to have a subtotal thyroidectomy. What's the best drug to decrease the vascularity of the gland?

A. Radioactive iodine	B. Levothyroxine	C. Lugol's solution	D. Liothyronine

3. A patient came to the clinic feeling lethargic, constipated, and cold. The patient was later diagnosed with hypothyroidism, what is the best choice of treatment for this patient?

A. Levothyroxine T4	B. Carbimazole	C. PTU	D. Bromocriptine

4. A patient came to the hospital suffering from weight gain and chronic fatigue. He was diagnosed with hypothyroidism.Which one of the following best choice of treatment?

A. Levothyroxine	B. Sermorelin	C. Lanreotide	D. Bromocriptine

5. By which mechanism is Levothyroxine exclusively metabolized?

A. Deamination	B. Iodination	C. Amination	D. Deiodination

6. A patient presented to the ER with tachycardia, shortness of breath, and chest pain, TSH levels was <0.01 normal range (0.04-4). The diagnosis of the thyroid storm was confirmed. What is the first line of treatment adjuvant to thyroid treatment

A. Propylthiouracil	B. Propranolol	C. Amiodarone	D. Radioactive iodine

1:A ,2C: , 3:A ,4:A ,5:D ,6:B

SAQ

1

mention the Disadvantages of radioactive iodine treatment to manage hyperthyroidism?

-Delayed hypothyroidism
-Cytotoxic actions: necrosis of follicular cells followed by fibrosis Genetic damage.
-Leukemia & neoplasia.

2

Hyperthyroidism Treatment Lines?

Thioamides (*antithyroid drugs*) → **Iodides** → **Radioactive Iodine** → **Adrenoceptor (β) Blockers** → **Surgery (Subtotal Thyroidectomy)**

3

Better to start therapy **before pregnancy** with, to avoid acute exacerbation during pregnancy?

^{131}**I** or subtotal **thyroidectomy**

drug of choice with pregnancy ? PUC (Propylthiouraci)

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Special thanks to Norah Almania for the amazing logo

Thyroid Storm

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- Plasmapheresis (rarely).

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