

Endocrine Block

Pharmacology Team 439

Color index:

Main Text

Important

Dr's Notes

Female Slides

Male Slides

Extra

Hyper & Hypothyroidism

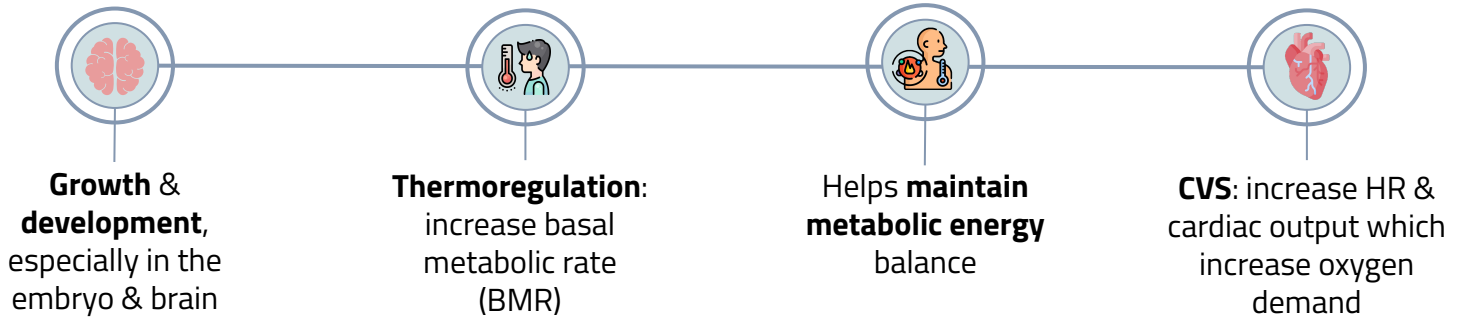
Objectives:

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

Hyperthyroidism

Thyroid function

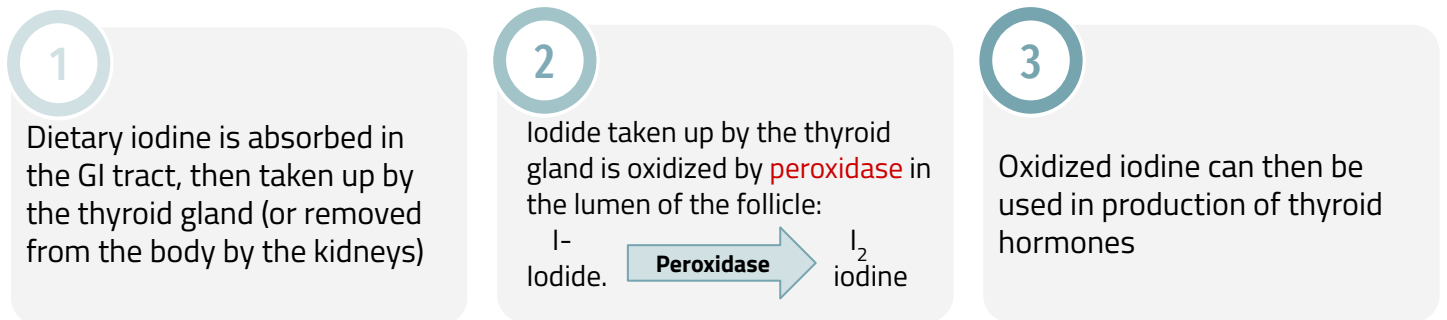
- Normal amount of thyroid hormones are essential for normal growth and development by maintaining the level of energy metabolism in the tissue.
- Either too little or too much thyroid hormones will bring disorders to the body.



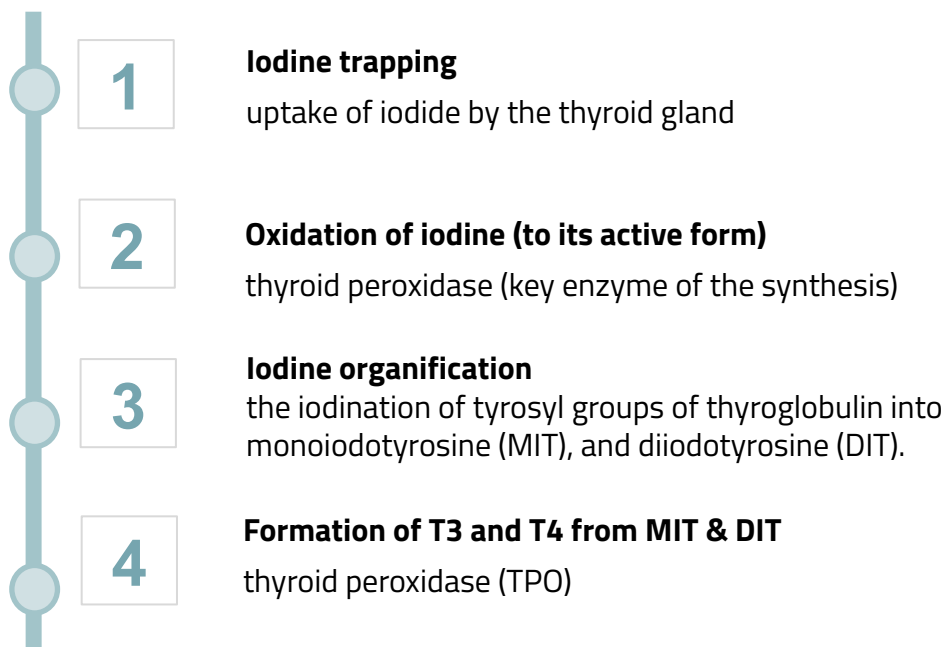
Iodine importance

- Thyroid hormones are unique biological molecules in that they incorporate iodine in their structure.
- Adequate iodine intake (diet, water) is required for normal thyroid hormone production.
- Major sources of iodine: - iodized salt - iodized bread - dairy products - shellfish
- Minimum requirement: 75 micrograms/day

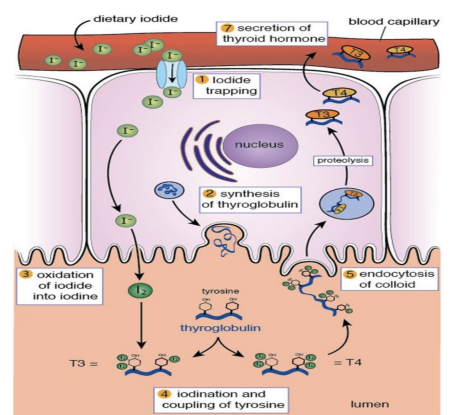
Iodine metabolism



Thyroid hormones synthesis

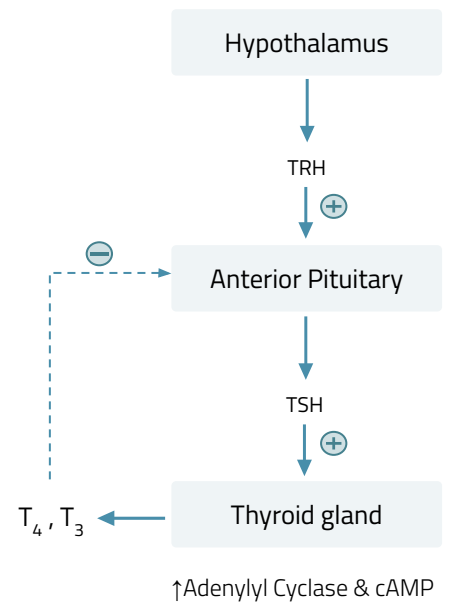


There are two biologically active thyroid hormones:
 -Triiodothyronine (T3)
 -Tetraiodothyronine (T4; thyroxine)



Thyroid regulation

- 1 Hypothalamus secretes Thyrotropin-Releasing Hormone (TRH) which stimulates synthesis and release of thyrotropin (Thyroid Stimulating Hormone or TSH) by the anterior pituitary.
- 2 TSH then stimulates the thyroid gland to uptake iodine, synthesize and release T₄ & T₃.
- 3 T₄ & T₃ levels feedback to both hypothalamus and pituitary affecting the release of TRH & TSH.
- 4 TSH release is influenced by hypothalamic TRH, and by thyroid hormones themselves.
- 5 Thyroid hormones exert negative feedback on TSH release at the level of the anterior pituitary.
 - Inhibition of TSH synthesis
 - Decrease in pituitary receptors for TRH



Thyroid hormone disorders

1 Hypothyroidism

Refers to disorders in which the thyroid gland secretes decreased amounts of hormones

2 Hyperthyroidism

- Refers to disorders in which the thyroid gland secretes increased amounts of hormones (increased thyroid hormones synthesis and secretion).
- All patients with hyperthyroidism have thyrotoxicosis.
- ↑ production of thyroid hormones by hyperfunctioning thyroid gland.¹

3 Thyrotoxicosis

- Is the term for all disorders with increased levels of circulating thyroid hormones.
- Hypermetabolic state caused by excess thyroid hormone at the tissue level.
- Not all patients with thyrotoxicosis have hyperthyroidism.
- ↑ thyroid hormones in the body because of any cause.¹

4 Thyroid neoplasia

Benign enlargement or malignancies of the gland

(1) Difference between Thyrotoxicosis and Hyperthyroidism (From Robbins). [Click here](#)

Causes of thyrotoxicosis



With high RAIU

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



With low RAIU

- Thyroiditis
- Iodine-induced thyrotoxicosis:
 - Drugs (e.g. Amiodarone)
 - antiarrhythmic drug amiodarone:
 - causes subacute thyroiditis.
 - leads to thyroid dysfunction (both hypo and hyperthyroidism).
 - Radiographic contrast media

radioactive iodine uptake: a test that quantifies the percentage of the administered amount of radioactive iodine taken up by only the functional parts of the thyroid gland. Read more [here](#)

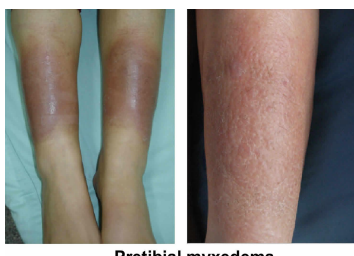
Features of diseases

Graves' Disease (diffuse toxic goiter)

Cause by thyroid stimulating immunoglobulins that stimulate TSH receptor, resulting in sustained thyroid over activity.

-Mainly in young adults aged 20-50
-5 times more frequent in women

-Swelling of soft tissues of hands and feet
-Clubbing of fingers and toes
-Half of cases have Exophthalmos (main feature of Graves' disease) (not seen with other causes of hyperthyroidism)
-5% have pretibial myxedema (thyroid dermopathy)



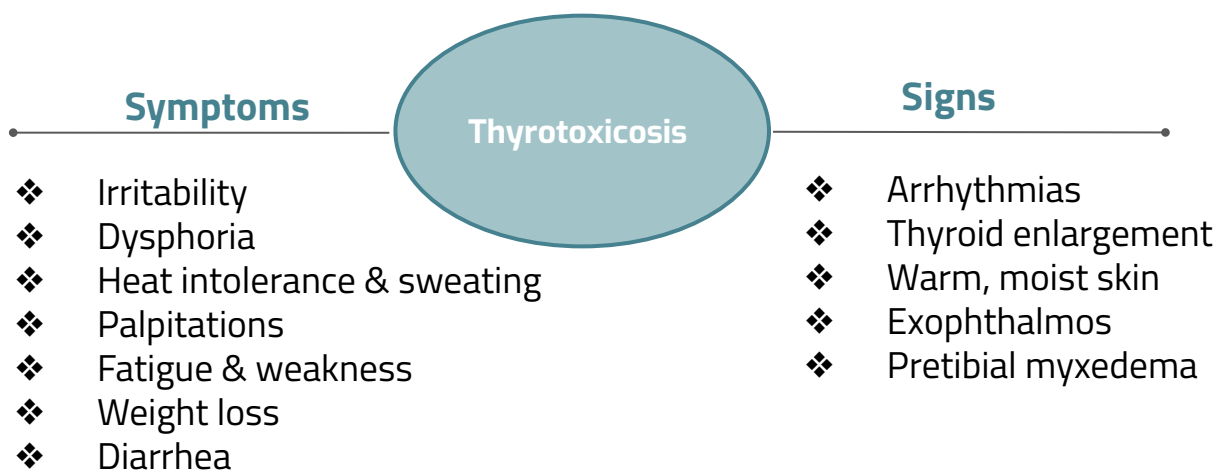
Pretibial myxedema

Toxic Multinodular Goiter

Second most common cause of hyperthyroidism

Most cases in women in 5th to 7th decades

-Often have long-standing goiter (chronic) -Symptoms usually develop slowly (50-70)



Treatment of hyperthyroidism



Thioamides

Drug	Propylthiouracil (PTU)	Methimazole\Carbimazole Carbimazole: prodrug converted to the active metabolite methimazole
M.O.A	<ul style="list-style-type: none"> Both PTU and Methimazole: Inhibits synthesis of thyroid hormones by inhibiting the peroxidase enzyme that catalyzes the iodination of tyrosine residues. ★ Additional Mechanism for PTU ONLY: blocks the conversion of T4 to T3 in peripheral tissues 	
P.k	<ul style="list-style-type: none"> Rapidly absorbed ★ Protein binding: 80-90% Accumulation: in thyroid Excreted by kidneys as inactive metabolite within 24 hours Half-life: 1.5 hours (short) Administered every 6-8 hours 	<ul style="list-style-type: none"> Rapidly absorbed ★ Protein binding: most of the drug is free Accumulation: in thyroid Excretion is slow, 60-70% of drug is recovered in urine in 48 hours Half-life: 6 hours (long) Administered every 8 hours
Pregnancy	<ul style="list-style-type: none"> Crosses placenta (Crossing placenta is less readily as it is Highly protein bound) ★ Recommended in pregnancy (FDA class D drug) very important to remember 	<ul style="list-style-type: none"> Concentrated in thyroid & crosses placenta ★ Not recommended in pregnancy
Breast feeding	<ul style="list-style-type: none"> Less secreted in breast milk ★ Recommended 	<ul style="list-style-type: none"> Secreted ★ Not recommended
ADRs	<ul style="list-style-type: none"> ★ Immunoallergic hepatitis(0.1-0.5%) (Almost exclusively in patients taking propylthiouracil) ANCA-positive vasculitis (Anti-neutrophil cytoplasmic antibodies) (rare) With propylthiouracil 	<ul style="list-style-type: none"> Abnormal sense of taste or smell (rare) with Methimazole only Methimazole preferred due its long half life and less side effect in compare to (PTU)
	<ul style="list-style-type: none"> Skin reactions (frequency: 4-6%): Urticarial or macular reaction Arthralgia (1-5%) GIT effects (1-5%): Gastric distress and nausea Polyarthritis (1-2%): So-called anti-thyroid arthritis ★ Agranulocytosis (0.1-0.5%): Seen in patients with Graves' disease; occurs within 90 days of treatment. 	

Note: The short plasma half-life of these agents (1.5 hours for propylthiouracil and 6 hours for methimazole) has little influence on the duration of the antithyroid action or the dosing interval because both agents are accumulated by the thyroid gland

If I asked you what is the drug of choice in the case of pregnancy? PTU

Iodine\ Iodide

Drug	1- Organic iodides: iopanoic acid or ipodate 2- Potassium iodide or lugol's solution
M.O.A	<ul style="list-style-type: none"> Inhibit thyroid hormone synthesis and release ★ Block the peripheral conversion of T4 to T3 ★ The effect is not sustained (produce a temporary remission of symptoms) Not use as maintenance therapy only rapid temporary remission
Uses	<ul style="list-style-type: none"> ★ Drug of choice Prior to thyroid surgery to decrease vascularity & the size of gland Following radioactive iodine therapy Thyrotoxicosis
C.I	<ul style="list-style-type: none"> ★ Should not be used as single therapy ★ Should not be used in pregnancy
ADRs	<ul style="list-style-type: none"> May produce iodism (rare, as iodine isn't much used now), iodism symptoms: skin rash, hypersalivation, oral ulcers, metallic taste, bad breath.

Radioactive Iodine (RAI)

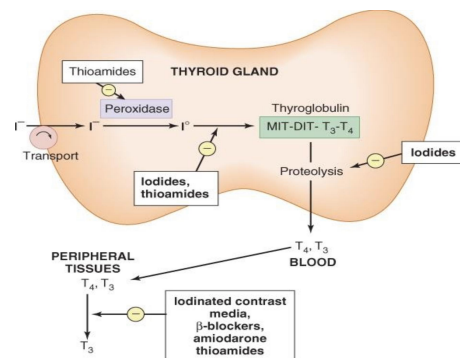
Drug	Radioactive Iodine (RAI)
M.O.A	<ul style="list-style-type: none"> ^{131}I (iodine) isotope (therapeutic effect due to emission of β rays) ★ Accumulates in the thyroid gland and destroys parenchymal cells, producing a long-term decrease in thyroid hormone levels.
P.k	<ul style="list-style-type: none"> Clinical improvement may take 2-3 months Half-life 5 days ★ Cross placenta & excreted in breast milk (not safe in pregnancy) Available as a solution or in capsules <p>Advantages:</p> <ul style="list-style-type: none"> Easy to administer, effective, painless and less expensive P.K <p>Disadvantages:</p> <ul style="list-style-type: none"> High incidence of delayed hypothyroidism may cause disruption of more follicles than intended leading to decrease thyroid hormone secretion even less than normal rate ★ Large doses have cytotoxic actions (necrosis of follicular cells followed by fibrosis) May cause genetic damage May cause leukemia & neoplasia
Uses	<ul style="list-style-type: none"> Hyperthyroidism mainly in old patients (above 40) Graves' disease Patients with toxic nodular goiter Can be used as a diagnostic method so its use as treatment and diagnosing in imaging study

β -blockers

Drug	Propranolol\ Atenolol\ Metoprolol
Uses	<p>Only use to treat the symptoms of sympathetic activation by thyroid hormone (ex: Cardiac symptoms)</p> <ul style="list-style-type: none"> Adjunctive therapy to relief the adrenergic symptoms of hyperthyroidism such as tremors, palpitation, heat intolerance and nervousness
C.I	<ul style="list-style-type: none"> Propranolol is contraindicated in asthmatic patients that why it's important to take history , Give selective β_1 in this case Not Non selective

Thyroidectomy

- Sub-total thyroidectomy is the treatment of choice in very large gland or multinodular goiter (done in case of severe hyperthyroidism in which the gland is >4 times the normal)



IMPORTANT :

Methimazole\Carbimazole preferred due its **long half life** and **less side effect** in compare to (PTU) BUT in case of **pregnancy, Propylthiouracil (PTU)** is drug of choice.

Special Conditions of Hyperthyroidism and their Management

Thyrotoxicosis during pregnancy

- Better to start therapy before pregnancy with ^{131}I or subtotal thyroidectomy to avoid acute exacerbation during pregnancy

During pregnancy:

- Radioiodine is contraindicated
- **Propylthiouracil is the drug of choice during pregnancy**

Thyroid Storm.

- It is a medical emergency of a sudden acute exacerbation of all the symptoms of thyrotoxicosis, presenting as a life-threatening syndrome.
- There is hypermetabolism, and excessive adrenergic activity, death may occur due to heart failure and shock.

Management of Thyroid Storm:

- 1 It should be treated in an ICU for close monitoring of vital signs and for access to invasive monitoring and inotropic support
- 2 **Correct electrolyte abnormalities**, treat cardiac arrhythmia (if present) & aggressively control hyperthermia by applying ice packs
- 3 Promptly administer **antiadrenergic drugs** (e.g. propranolol) to minimize sympathomimetic symptoms (**Life saving treatment**)
- 4 High-dose propylthiouracil (PTU) is preferred because of its early onset of action, but it has a **risk of severe liver injury and acute liver failure.**
- 5 Administer iodine compounds (Lugol's iodine or potassium iodide) orally or via a nasogastric tube.
- 6 Hydrocortisone 50 mg IV every 6 hours to prevent shock.
- 7 Rarely, plasmapheresis has been used to treat Thyroid Storm.

Management of Graves' Disease

Mild/Moderate Hyperthyroidism:

(small or moderately enlarged thyroid; children or pregnant or lactating women]

- Primary anti-thyroid drug therapy should be considered (**drug of choice**).
- Start methimazole, 5–30 mg/day, (**PTU preferred in pregnant women**)
- Monitor thyroid function every 4–6 wk until euthyroid state achieved
- Discontinue drug therapy after 12–18 mo
- Monitor thyroid function every 2 mo for 6 mo, then less **frequently. if:**

Relapse:

Definitive radioiodine (**Second course of anti thyroid drug therapy in children**)

Remission:

Monitor thyroid function every 12 mo indefinitely

Severe Hyperthyroidism:

[markedly elevated serum T4 or T3 very large goiter, > 4 times normal]

- Definitive therapy with radioiodine preferred in **adults**
- Normalization of thyroid function with anti-thyroid drugs before **surgery** in elderly patients and those with heart disease

-How the female doctor explained this:
firstly radioiodine then once thyroid function is normalized give antithyroid drugs before surgery.

Hypothyroidism

- Thyroid gland does not produce enough hormones
- May be congenital, primary or secondary
- Congenital: in children, hypothyroidism leads to delay in growth (dwarfism), and intellectual development (cretinism)
- People who are most at risk include those over age 50 & mainly in females
- Prevalence is 14/1000 females and 1/1000 males
- Diagnosed by low plasma levels of T3 & T4

causes of hypothyroidism

Primary : Inadequate function of the gland itself

- Iodine deficiency is the most common cause of primary hypothyroidism and endemic goiter worldwide
- Autoimmune: Hashimoto's thyroiditis
- Radioactive iodine treatment of hyperthyroidism
- Post thyroidectomy
- Anti-thyroid drugs (CMZ , PTU)
- Other drugs (lithium, amiodarone)
- Subacute thyroiditis
- Thyroid carcinoma

Goiter:

-abnormal growth of the thyroid gland.
-due to over and under production of thyroid hormones.

Endemic goiter:

Occur in certain areas due to not enough iodine in their diet.

Secondary :

- Hypothalamic disease
- Pituitary disease

Manifestations of hypothyroidism

Early

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

VS

Late

- Decreased sense of taste and smell
- Dry flaky skin
- Hoarseness
- Menstrual disorders
- Puffy face, hands, and feet
- Thinning of eyebrows

Sometime these manifestation overlap with aging

Treatment of hypothyroidism

Replacement therapy with synthetic thyroid hormone preparations :

Levothyroxine (T4)

Liothyronine (T3)

Liotrix
Mixture of T4 and T3

Drug	Levothyroxine (T4)
M.O.A	<ul style="list-style-type: none"> A synthetic form of the thyroxine (T4) is the drug of choice for replacement therapy <ul style="list-style-type: none"> Stable and has a long half life (7 days) Administered once daily. Restore normal thyroid levels within 2-3 weeks Absorption is increased when hormone is given on empty stomach (characteristic of this drug) (given in the morning 1h before breakfast). Metabolism: <ul style="list-style-type: none"> Major pathway of thyroid hormone metabolism is through sequential deiodination <ul style="list-style-type: none"> 80% of circulating T3 is derived from peripheral T4 by monodeiodination The liver is the major site of degradation for both T4 and T3 80% of the daily dose of T4 (levothyroxine) is deiodinated to yield equal amounts of T3 and rT3 (reverse T3, which is inactive)
Uses	<p>Hypothyroidism regardless of etiology:</p> <ul style="list-style-type: none"> Congenital Pregnancy (drug of choice) Hashimoto thyroiditis
Doses	<ul style="list-style-type: none"> Oral preparations available from 0.025 to 0.3 mg tablets Parenteral preparation 200-500µg given in a dose of 12.5 – 25 µg/day for two weeks and then increased every two weeks. Be Careful it's micro Not milligram
ADRs	<p>ADRs in OVERDOSE: giving T4 will show symptoms of hyperthyroidism</p> <ul style="list-style-type: none"> In children: <ul style="list-style-type: none"> Restlessness, insomnia Accelerated bone maturation In Adults: <ul style="list-style-type: none"> Cardiac arrhythmias (Tachycardia, atrial fibrillation) Tremor, restlessness, headache Heat intolerance Muscle pain Change in appetite, weight loss
Caution	<p>In old patients and in patients with cardiac problems , treatment is started with reduced dosage and then increased gradually after monitoring.</p>

Drug	Liothyronine (T3)
M.O.A	<p>Advantage:</p> <ul style="list-style-type: none"> More potent (3-4 times) rapid onset of action than levothyroxine <p>Disadvantage:</p> <ul style="list-style-type: none"> short half life - Not recommended for routine replacement therapy (requires multiple daily doses) Levothyroxine (T4) is drug of choice in this case due to long half life Should be avoided in Cardiac patients because it's more potent it increase risk of cardiac symptoms
Doses	<ul style="list-style-type: none"> Oral preparation available are 5-50µg tablets Parenteral use 10µg/ml

Comparison in P.K of the drugs

Drug	Liothyronine (T3)	Levothyroxine (T4)
Potency	4 (more potent)	1 less potent
T1\2 (days)	≤2 shorter	6-7 (longer)
Protein binding	99.5	99.96

Drug	Liotrix
M.O.A	Combination of synthetic T4 & T3 in a ratio 4:1 that attempt to mimic the natural hormonal secretion
Disadvantages	<p>The major limitations to this product are:</p> <ul style="list-style-type: none"> - High cost Disadvantages - Lack of therapeutic rationale because 35% of T4 is peripherally converted to T3

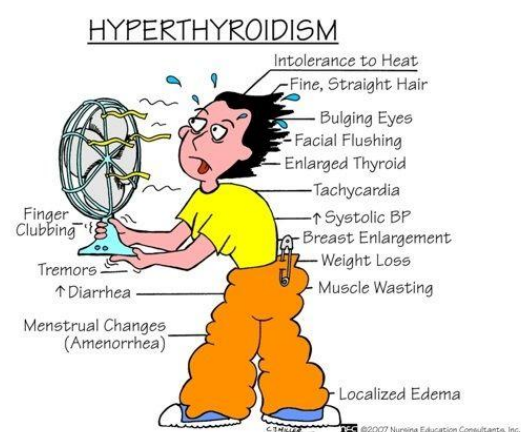
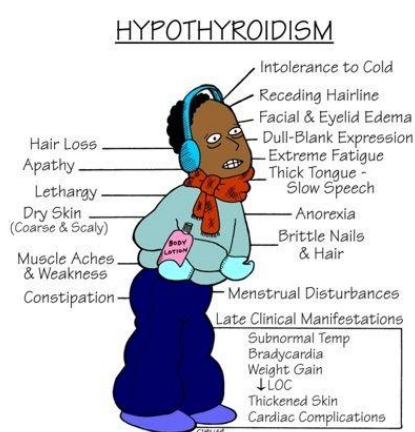
Special Conditions of Hypothyroidism and their Management

Myxedema Coma

- Life-threatening hypothyroidism
- The treatment of choice is **loading dose of levothyroxine intravenously** 300-400µg initially followed by 50µg daily **High Risk of Cardiac symptoms due to the high dose**
- I.V. liothyronine can be used for rapid response but it may **provoke cardiotoxicity**
- I.V. hydrocortisone may be used in case of adrenal and pituitary insufficiency.

Hypothyroidism in Pregnancy

- In pregnant hypothyroid patient **20-30% increase in thyroxine is required** because of :
 - elevated maternal thyroxine binding globulin (TBG) induced by **estrogen**
 - early development of **fetal brain which depends on maternal thyroxine.** (untreated hypothyroidism in mother leads to impaired brain development in the baby)..



Summary

Class	Drug	M.O.A	Uses	ADRs
Hyperthyroidism				
Thioamides (Antithyroid)	Propylthiouracil	Both PTU and Methimazole: Inhibits synthesis of thyroid hormones by inhibiting the peroxidase enzyme.	-Drug Of choice in pregnancy -Used for breastfeeding	-Skin reactions -Arthralgia -Gastric distress -anti-thyroid arthritis
	Methimazole Carbimazole	- PTU ONLY: blocks the conversion of T ₄ to T ₃ in peripheral tissues	Not used In pregnancy nor breastfeeding	-Agranulocytosis (in patients with Graves' disease)
Iodide/Iodine	1- Organic iodides: iopanoic acid or ipodate	-Inhibit thyroid hormone synthesis and release	-Prior to thyroid surgery	
	2-Potassium iodide or Lugol's solution	-Block the peripheral conversion of T₄ to T₃	- Following radioactive iodine therapy -Thyrotoxicosis	- iodism
Radioactive Iodine (RAI)	RAI	Accumulates In the thyroid gland and destroys parenchymal cells	-old patients (above 40) - can be used as a diagnostic method	Large doses have cytotoxic actions
Beta-Blockers	-Propranolol -Atenolol -Metoprolol	-	-Adjunctive therapy to relieve the adrenergic symptoms of hyperthyroidism	
Hypothyroidism				
Levothyroxine (T4)	Advantages: - stable - Long T _{1/2} - Once daily	The drug of choice for replacement therapy	overdose: - Children: restlessness, insomnia accelerated bone maturation - Adults: cardiac arrhythmia, tremor, restlessness, headache, weight loss, heat intolerance, muscle pain	- old patients - cardiac problems
Liothyronine (T3)	Advantages: - potent - Rapid response Disadvantages: - short T _{1/2}	-	-	- cardiac problems
Liotrix	Combo of T4.T3 mimic the natural secretion	-	-	-

MCQs

Q1: a drug that blocks the conversion of T4 to T3

A- PTU B-Methimazole C- Iodide iodine D- A and C

Q2: A 34-year-old patient who is 28 weeks pregnant with her first baby is referred to you as an emergency with newly diagnosed symptomatic hyperthyroidism. what's the drug of choice ?

A- Propylthiouracil B- Methimazole C- Potassium iodide D- RAI

Q3: A 25-year-old woman is diagnosed as having Graves disease with hyperthyroidism. She is prescribed carbimazole treatment, and she has a number of questions concerning the possible adverse effects. Which of the following serious adverse effects are most likely to occur after carbimazole

A- Iodism B- Renal failure C- Immunoallergic hepatitis D- Agranulocytosis

Q4: A patient is receiving radioactive iodine treatment for hyperthyroidism. Which of the following is most likely not a feared complication

A- Delayed hypothyroidism B- Agranulocytosis C- Genetic damage D- Leukemia

Q5: A patient is admitted with complaints of palpitations, excessive sweating, and unable to tolerate heat. Her medical history reveals that she has asthma. What is your drug of choice to relieve her cardiac symptoms

A- Propranolol B- Atenolol C- Enalapril D- Potassium iodide

Q6: A 43-year-old man was undergoing surgery to remove a very large nontoxic goiter, apparently due to iodide deficiency. A short course of potassium iodide was administered before surgery. Which of the following statements best explains why this drug was given to the patient?

A- To stimulate thyroid hormone synthesis before surgery B- To overcome iodine deficiency after surgery C- To reduce the size and vascularity of the thyroid gland D- To decrease the risk of hypothyroidism after surgery

Q7: A 50-year-old woman complained to her physician of fatigue, cold intolerance, weight gain, and constipation. Which of the following would be the most appropriate initial therapeutic step for this patient?

A- Levothyroxine B- Liothyroxine C- Potassium iodide D- Propranolol

Q8: A 64-year-old woman was admitted to the emergency department with the admitting diagnosis of myxedema coma. Which of the following drugs should be included in the emergency therapy of this patient?

A- IV Hydrocortisone B- IV Liothyronine C- Loading dose of levothyroxine intravenously D- :)

Q9: Which of the following best explains the primary reason for adjustment of the levothyroxine dose during pregnancy?

A- To avoid maternal preeclampsia B- elevated maternal (TBG) C- To maintain normal fetal brain development D- B and C

1	2	3	4	5	6	7	8	9
D	A	D	B	B	C	A	C	D

SAQ

- Q1) a 44-year-old woman complains of palpitations, excessive sweating and weight loss. She was diagnosed with hyperthyroidism.**
- Mention 3 drugs that can be used to treat hyperthyroidism**
 - Mention the MOAs of drugs mentioned in Qa**
 - Mention the possible indicated uses for each drug mentioned in Qa**

- Q2) A 35-year-old man presented with lethargy, weight gain, and muscle weakness. Lab findings confirm the diagnosis of hypothyroidism.**
- In the treatment of hypothyroidism, levothyroxine is preferred over liothyronine. why?**
 - What hormone is produced in the peripheral tissues when levothyroxine is administered?**
 - List three ADRs of levothyroxine**

Answers

A1) a) Propylthiouracil, Iugol's solution, Radioactive Iodine (RAI)

b) Propylthiouracil: inhibiting the peroxidase enzyme and blocks the conversion of T₄ to T₃ in peripheral tissues, Iugol's solution: Inhibit thyroid hormone synthesis and release and Block the peripheral conversion of T₄ to T₃ Radioactive Iodine (RAI): Accumulates In the thyroid gland and destroys parenchyma

c) Propylthiouracil: Drug Of choice in pregnancy

Iugol's solution: Prior to thyroid surgery

Radioactive Iodine (RAI): old patients

A2) a) Levothyroxine is (Stable and has a long half life (7 days), Administered once daily, Restore normal thyroid levels within 2-3 weeks) while liothyronine has short half life - Not recommended for routine replacement therapy (requires multiple daily doses)

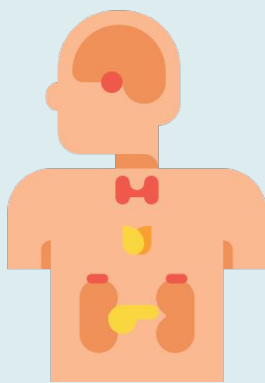
b) Levothyroxine (T₄) is converted into T₃ in the periphery

c) In Adults: Cardiac arrhythmias (Tachycardia, atrial fibrillation), Tremor, Heat intolerance



Feedback Form

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Endocrine Block

Pharmacology Team 439

Leaders

Banan AlQady

Ghada AlOthman

Nawaf Alshahrani

Organizers

- Duaa Alhumoudi
- Ghada Aljedaie
- Mais Alajami
- Mayasem Alhazmi
- Shatha Aldhohair
- Shayma Alghanoum
- Tarfah Alsharidi

Note Takers

- Abdulaziz Alrabiah
- Abdullah AlAnzan
- Duaa Alhumoudi
- Homoud Algadheb
- Yasmine Alqarni

Revisers

- Dana Naibulharam
- Hamad Almousa
- Omar Alhalabi

Members

- Abdulaziz Alderaywsh
- Abdulaziz Alghuligah
- Fatimah BinMeather
- Feras Alqaidi
- Ghada aljedaie
- Maha alanazi

- Manal AlTwaim
- Mona alomiriny
- Norah Almasaad
- Noura Bamarei
- Rand AlRefaei
- Salem alshihri

- Sarah AlQahtani
- Sarah Alaidarous
- Sarah Alobaid
- Shahd Almezel
- Yara Alasmari

