جامعة الملك سعود
King Saud University

Pharmacology
435 team

Drugs used in Hyper- & Hypo-thyrodism

Objectives:

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

Done by:

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Drug's name | Doctors' notes | Important | Extra

« لو أن الناس كلما استصعبوا أمرًا تركوه؛ ما قام للناس دنيا ولا دين! »
عمر بن عبدالعزيز

Anti-Hyperthyrodism | Mind Map

Treatment of Hyperthyroidism

Thioamides (Anti-thyroid drugs)

- Propylthiouracil
- Methimazole
- Carbimazole

Inhibit synthesis of thyroid hormones by inhibiting the peroxidase enzyme that catalyzes the iodination of tyrosine residues
Propylthiouracil blocks the conversion of T4 to T3 in peripheral tissues

Iodides

- Organic iodides.
- Potassium iodide.

- Inhibit thyroid hormone synthesis and release
- Block the peripheral conversion of T_4 to T_3

Radioactive iodine

^{131} I isotope

Accumulates in the thyroid gland and destroys parenchymal cells

Beta blockers

- Propranolol
- Atenolol
- Metoprolol

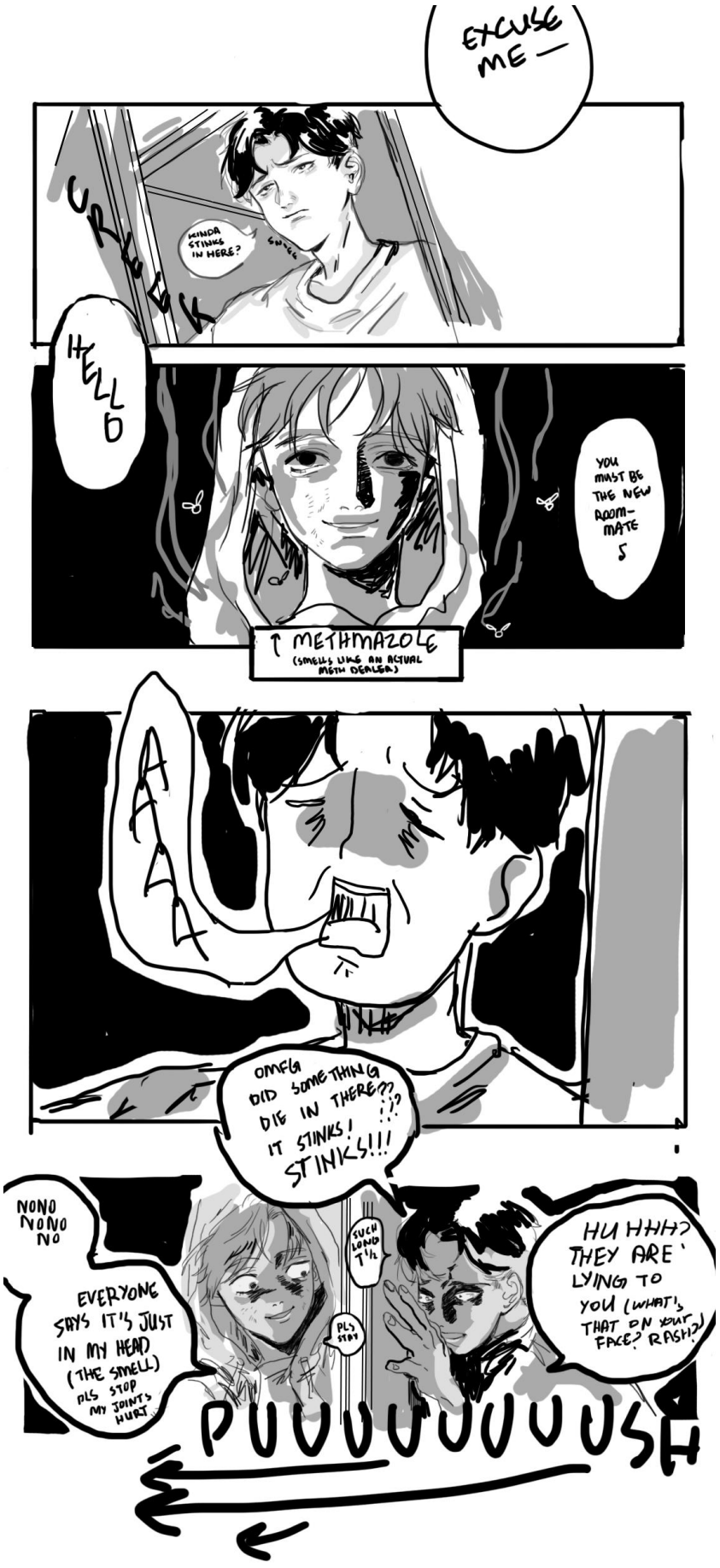
Adjunctive therapy to relief the adrenergic symptoms of hyperthyroidism

Surgery

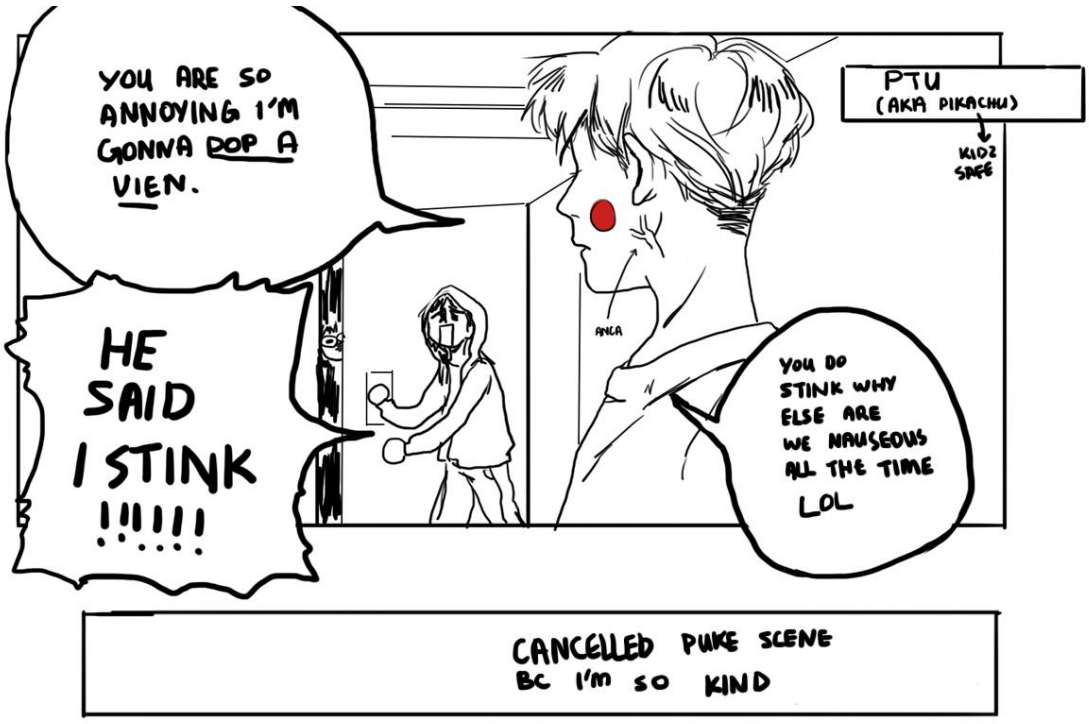
Treatment of hyperthyroidism:

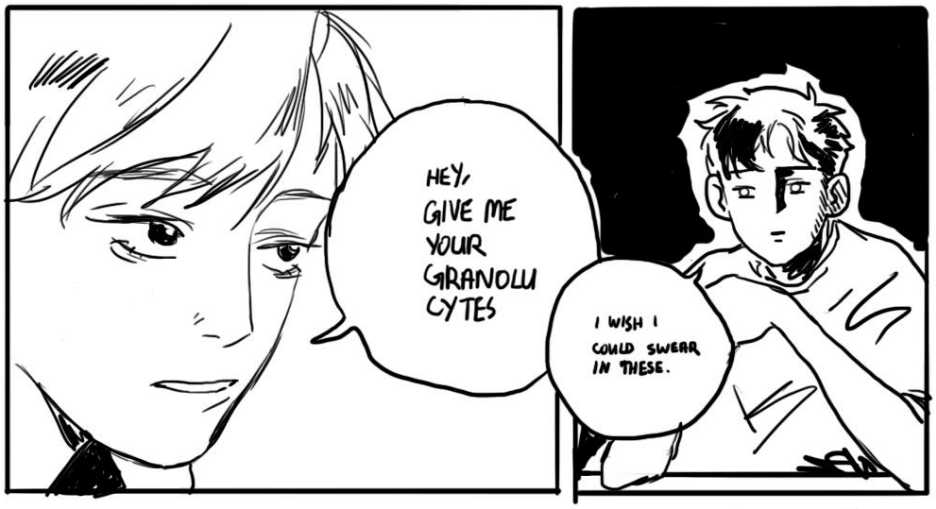
1. Removal of part or all of the thyroid: This can be accomplished either surgically or by destruction of the gland by radioactive iodine(131I)
2. Inhibition of thyroid hormone synthesis by thioamides
3. Blockade of hormone release by iodides

Comic! - 1


EXCUSE ME—
KNOCK
KINDA STINKS IN HERE?
SNIFF
HELLO
YOU MUST BE THE NEW ROOM-MATE ;)
↑ METHMAZOLE
(SMELLS LIKE AN ACTUAL METH DEALER)
OMFG DID SOMETHING DIE IN THERE?? !!? IT STINKS! STINKS!!!
NONO NONO NO
EVERYONE SAYS IT'S JUST IN MY HEAD (THE SMELL) PLS STOP MY JOINTS HURT
SUCH LOUD T½
PLS STOP
HUHHH? THEY ARE LYING TO YOU (WHAT'S THAT ON YOUR FACE? RASH?)
PUUUUUUUUUSH

Comic! - 2





@435kid

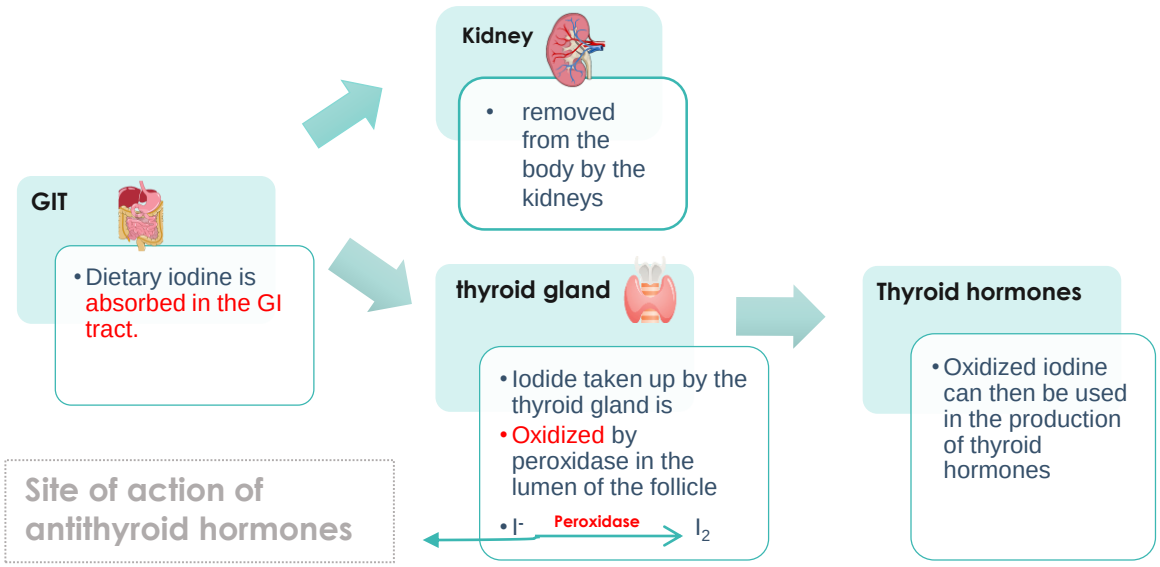
Done by Shadn Alomran ☺

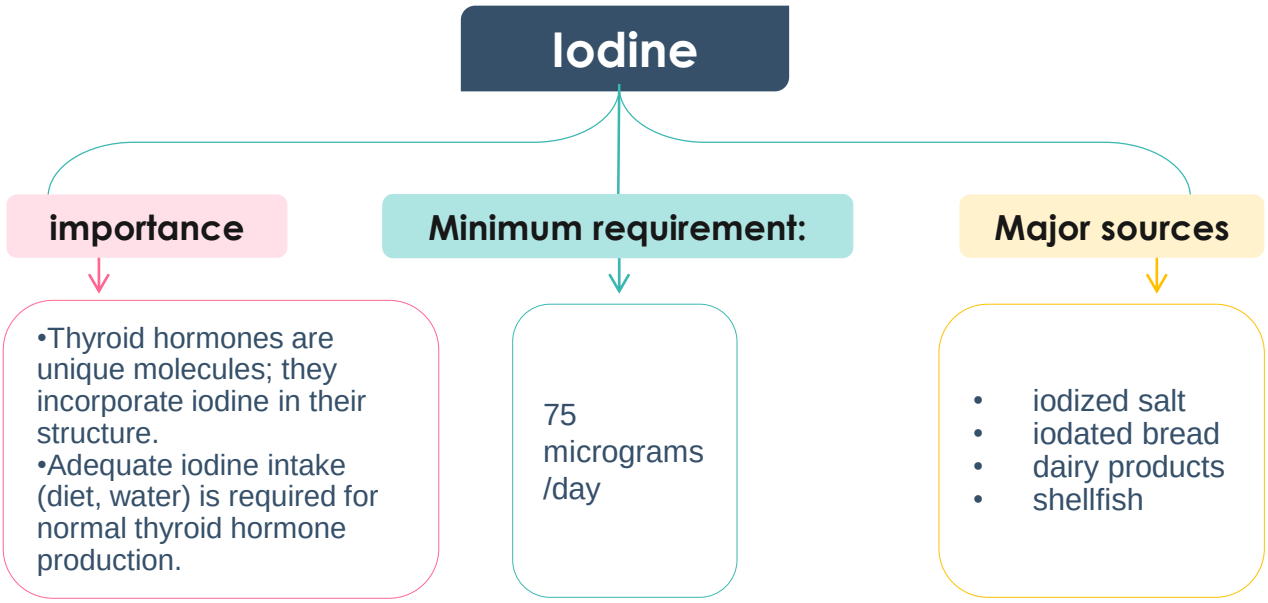
To Understand Better

Thyroid functions:

- **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.
- Growth & development, especially in the embryo & brain,
- Thermoregulation: increase basal metabolic rate (BMR),
- Helps maintain metabolic energy balance.
- CVS: increase HR & cardiac output which increase oxygen demand**.**

Iodine metabolism:

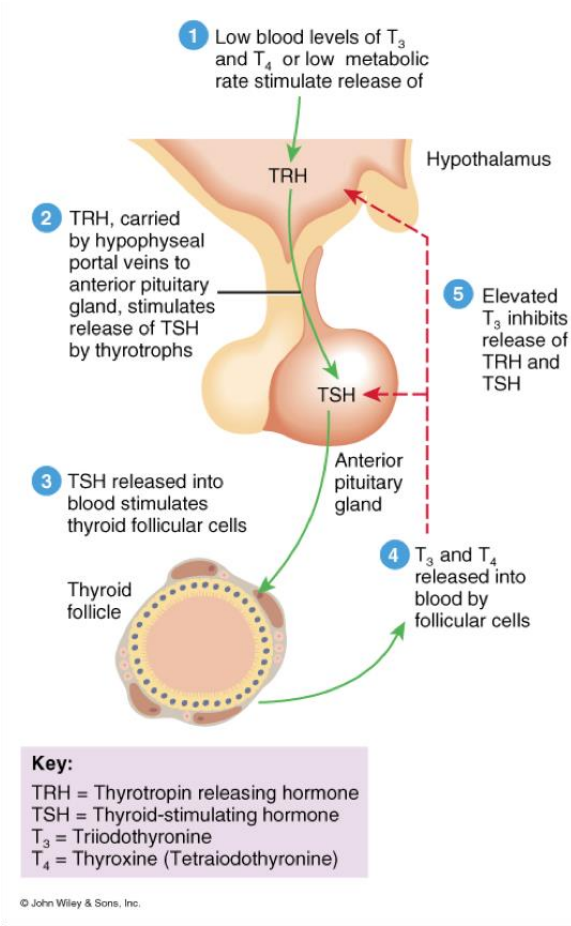




To Understand Better

Thyroid regulation:

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



There are **two** biologically **active** thyroid hormones:

Tetraiodothyronine (T4; thyroxine)

Tyrosine $\xrightarrow{+I}$ tetraiodothyronine (2tyrosine + 4I)

Triiodothyronine (T3)

Tyrosine $\xrightarrow{+I}$ triiodothyronine (2tyrosine + 3I)

To Understand better

Thyroid metabolism

Thyroid hormone production (7:17 min)

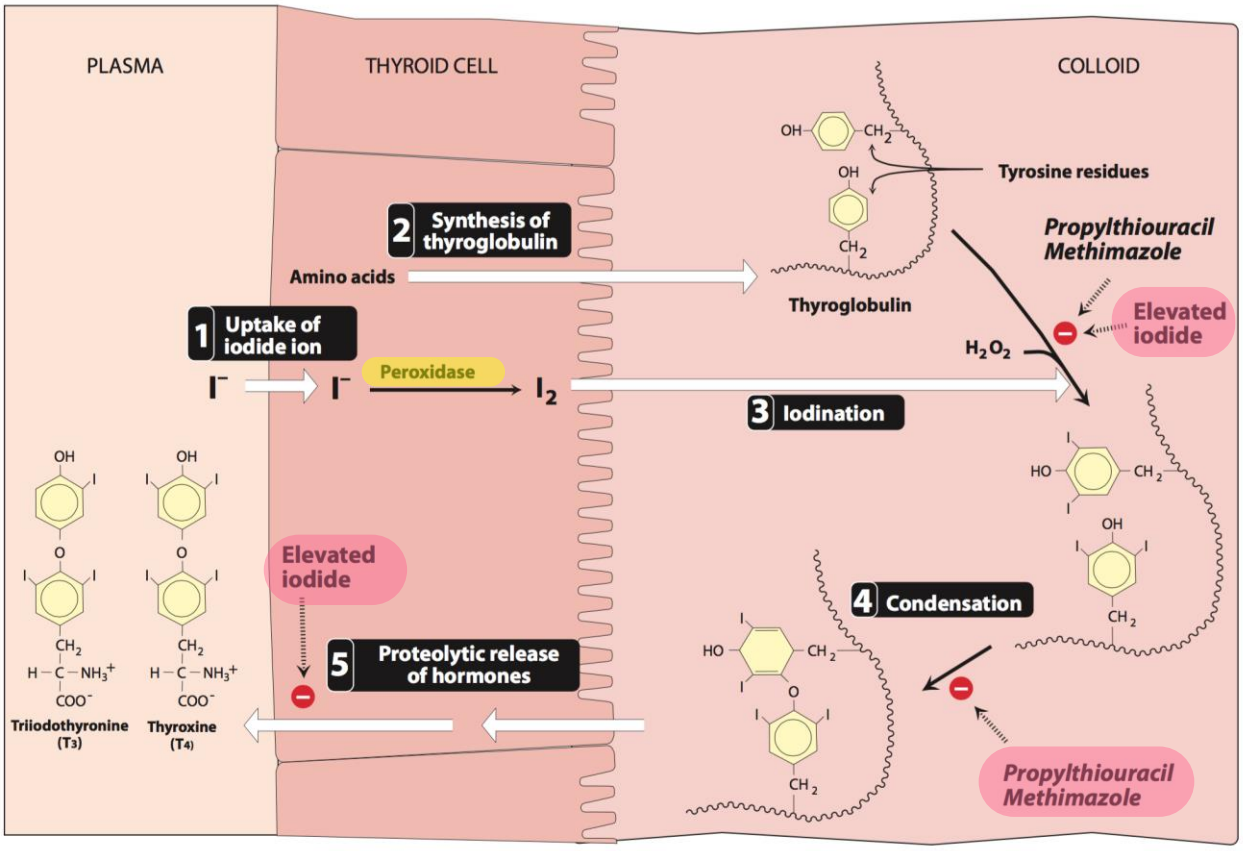


Figure 23.6
Biosynthesis of thyroid hormones.

This pic is very helpful in pharma part

Thyroid hormones disorders:

Thyrotoxicosis: Is the term for all disorders with increased levels of circulating thyroid hormones

Hyperthyroidism: Refers to disorders in which the thyroid gland secretes increased amounts of hormones

Thyroid hormone disorders:

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

Thyroid neoplasia: Benign enlargement or malignancies of the gland

To Understand Better

Thyrotoxicosis:	Hyperthyroidism
Hypermetabolic state caused by thyroid hormone excess at the tissue level.	Increased thyroid hormones synthesis and secretion
Not all patients with thyrotoxicosis have hyperthyroidism	All patients with hyperthyroidism have thyrotoxicosis

Causes of **thyrotoxicosis**:

Stick to pathology lecture in this point!

With high RAIU*

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

* RadioActive Iodine Uptake

With low RAIU

- Thyroiditis inflammation of the thyroid
- Iodine-induced thyrotoxicosis
  - drugs (e.g. amiodarone)
  - radiografic contrast media

Features of **Graves' disease**:

- Caused by thyroid stimulating immunoglobulins that stimulate TSH receptor , resulting in sustained thyroid over activity
- Mainly in young adults aged 20 to 50
- 5 times more frequent in women
- 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)

To Understand Better

Features of toxic multi-nodular goiter:

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

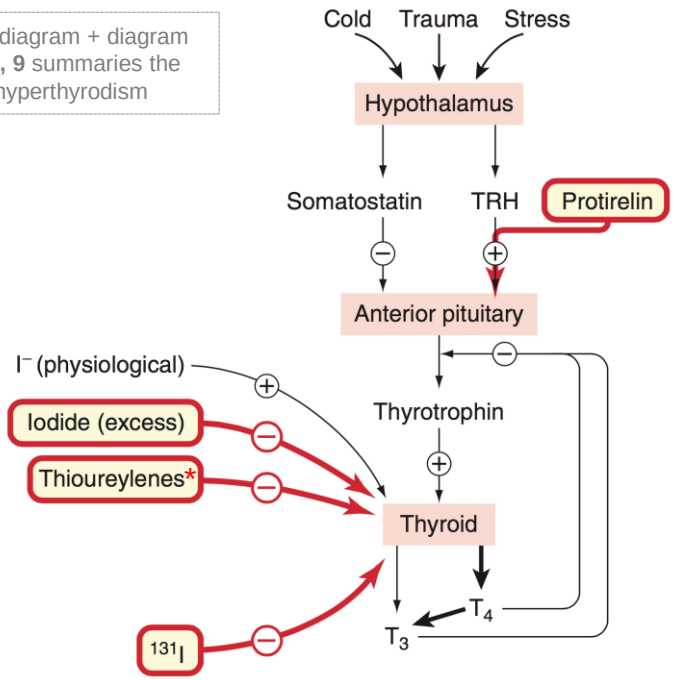
هذي الأعراض والعلامات هي اللي بتجي في السيناريو وتعرفون إن عنده هيبرثايرودزم

Thyrotoxicosis:	
Symptoms	**Signs**
Irritability	arrhythmias
Dysphoria	Thyroid enlargement
Heat intolerance & sweating	Warm, moist skin
Palpitations	Exophthalmus
Fatigue & weakness	Pretibial myxedema
Weight loss	
Diarrhea	

Treatment of hyperthyroidism

- **Thioamides** (antithyroid drugs)
- **Iodides**
- **Radioactive iodine**
- **Beta blockers**
- **Surgery "Thyroidectomy "**

This diagram + diagram in **p5, 9** summaries the anti-hyperthyrodism



* Sub-total thyriodectomy is the **treatment of choice** in **very large gland** or **multinodular goiter**.

* Thioureylenes = Thioamides

1- Thioamides

Drug	Propylthiouracil (PTU) Mnemon.: ITS PROPER IN PREGNANCY (use it)	Methimazole & Carbimazole (carbimazole is a prodrug converted to the active metabolite methimazole)
MOA	**Inhibit** synthesis of thyroid hormones by **inhibiting** the **peroxidase** enzyme that catalyzes the iodination of tyrosine residues (blocking iodine organification).	
	PTU (but **not** methimazole) blocks the conversion of T4 to T3 in peripheral tissues. ناخذ بالنا كويس إن: PTU has 2 actions, while Methimazole has ONLY **one** action! مهم جدًا.	Mnemonic: اسمه ميث ما ازول يعني كانه يقول لك أنا ما ازول لذلك يطلع من الجسم ببطء ولديه هاف لايف 6 ساعات وبما إنه ما يزول أكيد ما بعطيه وحدة حامل، كمان بما إنه ما يزول فيبقى له طعم ورائحة.
P.K	في الفارماكوكاينتكس أهم شيء نركز على **الفروقات بين الدوائين (بالأحمر).** - Rapidly absorbed. كلهم عندهم هالخاصية - **80-90% protein binding**. → وش نستفيد؟ يعني على إنه يدخل على البلاسينتا، إلا إنه يدخل بكميات **ضئيلة جدًا** بسبب إنه فيه بروتين ماسكه عشن لا يدخل بكميات كبيرة. عشان هالسبب، هو يستخدم في حالة الحوامل والمرضعات. - Accumulate in thyroid. - Execrate in kidney as inactive metabolite within 24h. - **Short half life** (1.5hrs). - Administration every 6-8 hrs. - **Crosses placenta** → (Crossing placenta is **less readily** as it is highly protein bound) **- Less secreted in breast milk.** مثل ما قلنا، لأنه ماسك ببروتين فما يدخل كثير في حليب المرضع.	- Rapidly absorbed. - **Most of the drug is free.** (not bind to a plasma protein, More active) - Accumulate in thyroid. - **Excretion slow, 60-70% of drug is recovered in urine in 48 hrs.** - **Long half life** (6hrs). - Administration every 8 hrs. - **Concentrated in Thyroid.** - **Crosses placenta & Secreted in breast milk** → low protein binding → increase entering through the placenta & milk.
Uses	- Recommended in pregnancy. - Recommended in breast feeding.	- The drug of choice in adults and children (more potent than PTU)
C.I		Not recommended in **pregnancy** (produces **teratogenic** effect) Not recommended in **breast feeding.**

1- Thioamides (Cont.)

Adverse Effects of thioamides

Agranulocytosis نهتم بايه يا قماعة؟

Adverse effect	Freq.	comments
Skin reactions	4–6%	**Urticarial** or **macular reactions** Both drugs have the same side effect
Arthralgia	1–5%	Both drugs have the same side effect
Polyarthritis	1–2%	So-called anti-thyroid arthritis Both drugs have the same side effect
GIT effects	1–5%	gastric distress and nausea Both drugs have the same side effect
Immunoallergic hepatitis	0.1–0.5%	Almost exclusively in patients taking **propylthiouracil**
Agranulocytosis → Patients should be watched for the risk of increased infections.	0.1–0.5%	Seen in patients with **Graves' disease**; occurs within 90 days of treatment نهتم بأه بالقرانيلوسيتوسز لأنها بتجي في كل الدوائين
ANCA-positive vasculitis (Anti-neutrophil cytoplasmic antibodies)	Rare	**With propylthiouracil**
Abnormal sense of taste or smell	Rare	**With methimazole only**

Warnings

Agranulocytosis	Congenital Malformations
Patients on **PTU** or **methimazole** should be instructed to immediately report to their physicians any symptoms suggestive of agranulocytosis, such as **fever** or **sore throat**.	**Methimazole** crosses the placental causing fetal harm, when administered in the first trimester of pregnancy.

2- IODINE (Lugol's solution, potassium iodide)

e.g.

- ✓ **Organic iodides as: iopanoic acid or ipodate**
- ✓ **Potassium iodide.**

MOA

- **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)

Uses

- **Prior to thyroid surgery** to decrease vascularity & size of the gland. → Preoperatively for 10-15 days.
- Following radio-active iodine therapy. → RAI could be used as treatment or for dx.
- Thyrotoxicosis. → Not used as 1st line treatment.

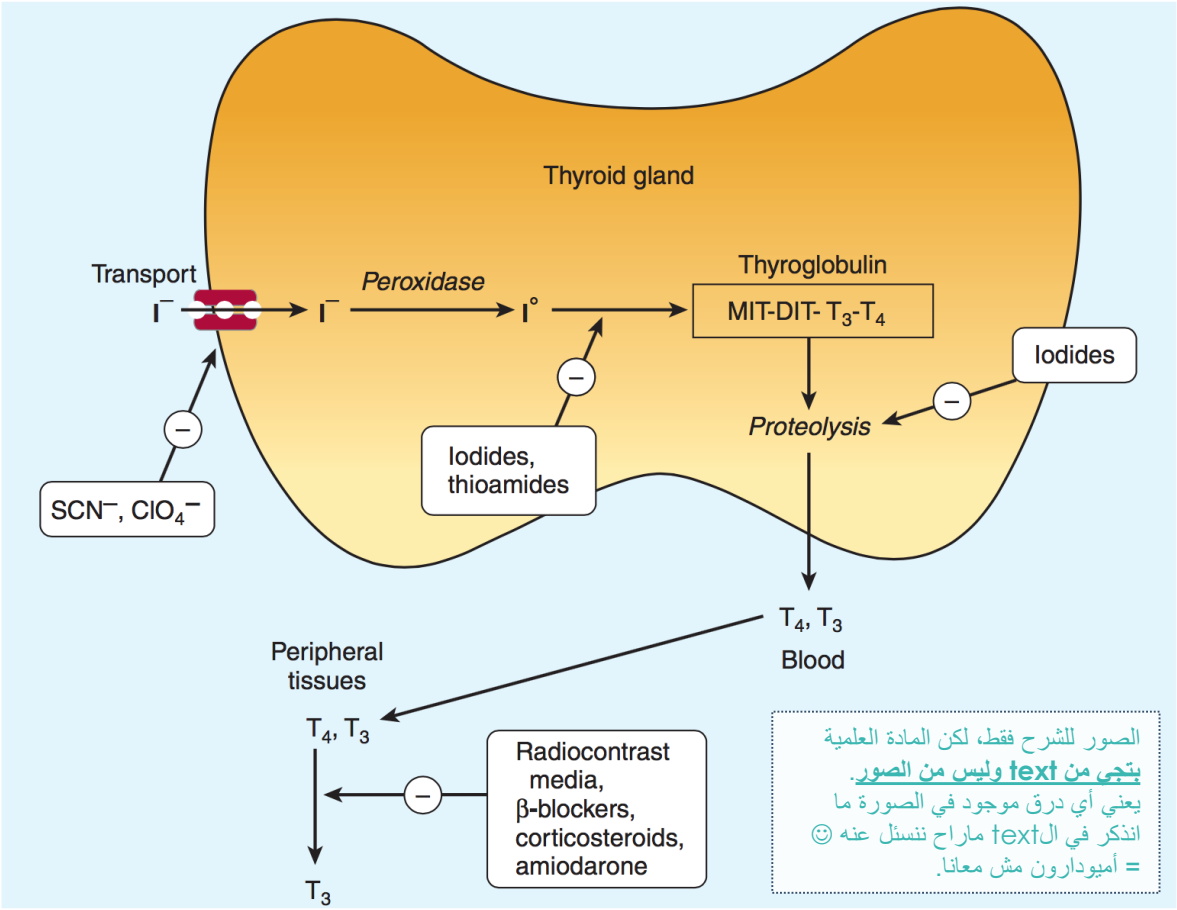
C.I

- Should not be used as a single therapy.
- **Should not be used in pregnancy.** → مهم
- May produce iodism (Rare, as iodine is not much used now)

Toxicity

- **Iodism Symptoms:** (resulted from high dose)

  Skin rash, hypersalivation, oral ulcers, metallic taste, bad breath.



الصور للشرح فقط، لكن المادة العلمية بتجي من text وليس من الصور.
يعني أي درق موجود في الصورة ما انذكر في الtext ماراح ننسئل عنه ☺
= أميودارون مش معانا.

3- Radioactive iodine (RAI)

MOA

- ^{131} I isotope (therapeutic effect due to **emission of β rays**)*

*__Accumulates in the thyroid gland and destroys parenchymal cells__, producing a **long-term decrease** (opposite to iodine) in thyroid hormone levels.

P.K

- **Clinical improvement may take 2-3 months.**
- Half-life 5 days.
- **Cross placenta & excreted in breast milk**. → حتى الآن إيش الأدوية الصالحة مع الحوامل والمرضعات؟ **PTU**
- Easy to administer, effective, painless and less expensive.
- Available as a solution or in capsules.

Uses

- Hyperthyroidism mainly in **old patients** (above 40).
- Graves' disease.
- Patients with toxic nodular goiter.
- As a **diagnostic**. (in low doses)

Disadvantages

- High incidence of delayed hypothyroidism. Conversion from hyperthyroidism to hypothyroidism.
- Large doses have cytotoxic actions (**necrosis of the follicular cells** followed by fibrosis) → in high dose.
- May cause genetic damage. (bc it is a radiation)
- May cause leukemia & neoplasia. (have not been realized after more than 50 years of clinical experience)
  - Should **not** be administered to **pregnant women** or **nursing mothers** (bc it crosses the placenta to destroy the fetal thyroid gland and is excreted in breast milk)

4- Adrenoceptor blocking agents

e.g. Propranolol, Atenolol, Metoprolol

MOA

- Mnemon.: (no -L) NOT IN LUNG PROBLEM like asthma.
- Adjunctive therapy to **relief the adrenergic symptoms** of hyperthyroidism **such as tremor, palpitation, heat intolerance and nervousness.**
  - Propranolol is used to control clinical symptoms of sympathetic overactivity in hyperthyroidism, perhaps by inhibiting conversion of thyroxine (T4) to triiodothyronine (T3).

C.I

- **Asthmatic patients** → in case of **Propranolol** → **In asthmatic patients we use Atenolol or Metoprolol.**

Thyrotoxicosis during pregnancy

- Better to start therapy **before** pregnancy with:
  - ✓ ^{131}I or **subtotal thyroidectomy** to avoid acute exacerbation during pregnancy.
- **During pregnancy:**
  - ★ **Propylthiouracil** is the **drug of choice** during **pregnancy.**
  - ✓ **Radioiodine is contraindicated.**

Thyroid storm

Thyroid storm

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

Management of thyroid storm

- Should be treated in an **ICU** for close monitoring of vital signs and for access to invasive monitoring and inotropic support.
- Start to treat the symptoms. **Correct electrolyte abnormalities**, Treat cardiac arrhythmia (if present) & Aggressively control hyperthermia by applying **ice packs**.
- Promptly administer **antiadrenergic drugs** (e.g. propranolol) to minimize sympathomimetic symptoms. Propranolol C.I in asthmatic patients, we use Atenolol, Metoprolol.
- High-dose Propylthiouracil (PTU) is **preferred** because of its early onset of action (risk of severe liver injury and acute liver failure).
- Administer **iodine** compounds (Lugol's iodine or potassium iodide) orally or via a nasogastric tube.
- **Hydrocortisone** 50 mg IV every 6 hours to **prevent shock**.
- Rarely, plasmapheresis has been used to treat thyroid storm.

Management of hyperthyroidism due to Graves' disease

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.**

إذن ممكن نعطي RAI أو
Anti-thyroid drugs

Mild/moderate hyperthyroidism

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

Primary **anti-thyroid** drug therapy should be considered

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 ما نوقف قبل سنة!

Monitor thyroid function every 2 mo for 6 mo, then less frequently

Relapse

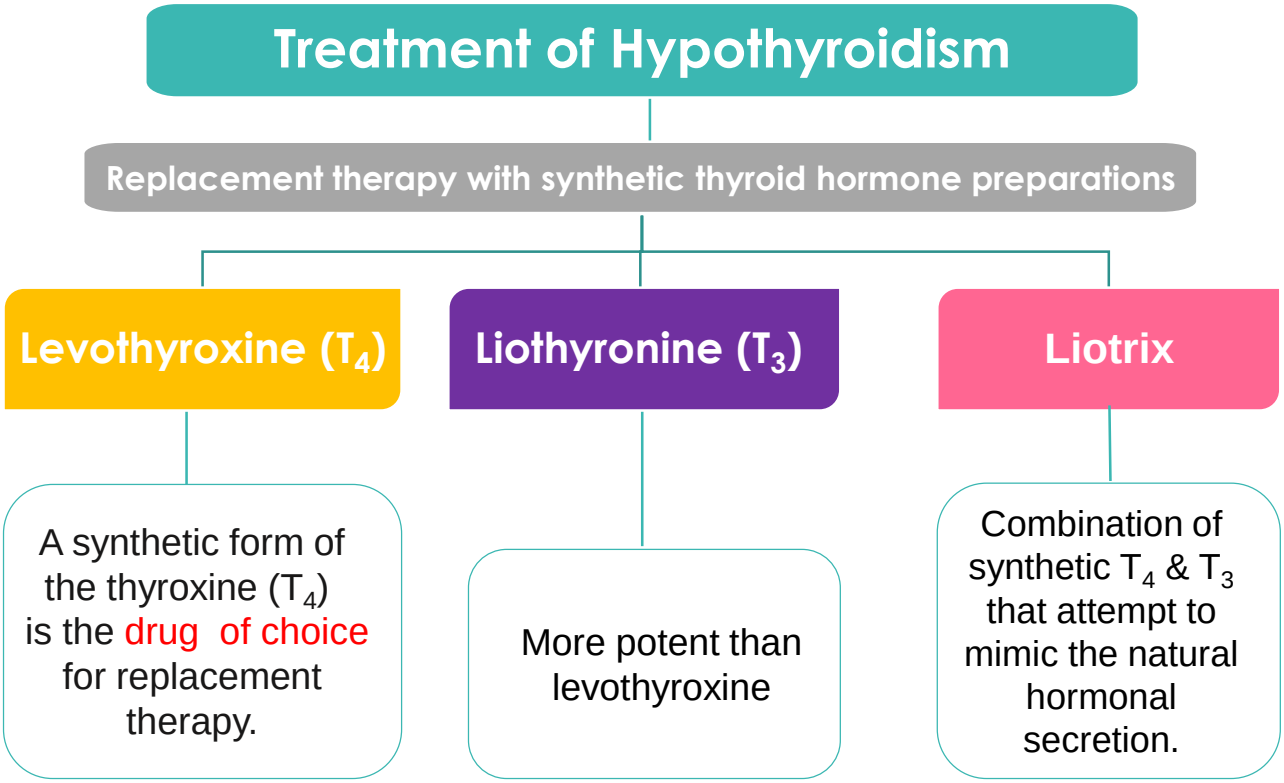
Definitive radioiodine therapy in **adults**. (Second course of anti-thyroid drug therapy in children)

Remission

Monitor thyroid function every 12 mo indefinitely.

عشان ما تتلخبطون إيش تستخدمون أنتي ثيرود والا راديوأيودين، فالسلايد دي بتبين لكم ممكن نستخدمهم كلهم، أما الشيء اللي أهتم له وأستخدم حاقة عن حاقة هو في حالة الحمل

Anti-Hypothyrodism | Mind Map



To Understand Better

Hypothyroidism:

- Thyroid gland does not produce enough hormones. Decrease in T3 and T4
- 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 and TSH.

To Understand Better

Types of hypothyroidism:

Primary hypothyroidism	Secondary hypothyroidism
❖ **Inadequate function of the gland itself – causes:** ○ **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 (Carbimazole) , PTU) ○ Other drugs (**lithium***, **amioderone**) *may cause goiter. ○ Sub-acute thyroiditis. ○ Thyroid carcinoma.	❖ **Hypothalamic disease.** ❖ **Pituitary disease.**

Manifestations of hypothyroidism

Early Manifestations of Hypothyroidism

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

Late Manifestations of Hypothyroidism

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

Treatment of Hypothyrodism

❖ **Replacement therapy** with synthetic thyroid hormone preparations:

Levothyroxine (T_4) | **Liothyronine (T_3)** | **Liotrix**

Levothyroxine (T4)

P.K

- **Mnemon.:** LEAVE IT ALONE IN THE STOMACH (give it ON EMPTY STOMACH)
- **Oral** preparations available from 0.025 to 0.3 mg tablets.
- **Parenteral** preparation 200-500µg.
- Levothyroxine is given in a dose of 12.5 – 25 µg/day for two weeks and then increased every two weeks.

★ A synthetic form of the thyroxine (T4) = Levothyrocine, is the **drug of choice for replacement therapy.**

- Stable and has a **long half life** (7 days).
- Administered **once daily**. → stable, has a long half life.
- Restore normal thyroid levels within 2-3 weeks.
- Absorption is increased when hormone is given on empty stomach. Is absorption increases with food? No, it **DECREASES**. يؤخذ قبل الفطور

Uses

- **Hypothyroidism**, regardless of etiology, including: in All cases of hypothyrodism
  - Congenital. - Hashimoto thyroiditis. - Pregnancy.

Metabolism

- Major pathway of thyroid hormone metabolism is through sequential **deiodination**
- 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 is deiodinated to yield equal amounts of T3 and rT3 (reverse T3, which is inactive)

ADRs (Over Dose)

❖ **Children:**
- Restlessness, insomnia, accelerated bone maturation.

❖ **Adults:** بشكل عام، يتحول لأعراض الهايبر لأنه زادت الثايرود هرمونز
- Cardiac arrhythmias → Mnemon.: T4 (THE HEART HAS 4 CHAMBERS) IN ADULTS CAUSES ARRHYTHMIA.
  - (Tachycardia, atrial fib.)
- Tremor, restlessness, headache.
- Heat intolerance. Opposite to the manifestation.
- Muscle pain.
- Change in appetite, weight loss.

C.I

- In **old patients** & Patients with **cardiac problems:**
  - ✓ Treatment is started with **reduced dosage**.

Treatment of Hypothyrodism (cont.)

Drug	Liothyronine (T3)	Liotrix
P.K	○ **More potent** (3-4 times) and **rapid** action than levothyroxine. ○ **oral** preparation available are 5-50µg tablets. ○ **Parenteral** use10µg/ml. ○ Has a **short half life** → not recommended for routine replacement therapy (requires multiple daily doses) → bc ot this, levothyrocine is better.	○ Combination of synthetic T4 & T3 in a ratio 4:1 that attempt to mimic the natural hormonal secretion. ○ The major limitations to this product are **high cost** and **lack of therapeutic rationale** because 35% of T4 is peripherally converted to T3.
C.I	○ Should be avoided in **cardiac patients**.	

Pharmacokinetic of Thyroid Hormones

Hormone	Biologic Potency	$t_{1/2}$(days)	Protein Binding (%)
Levothyroxine (T_4)	1	**6-7**	99.96
Liothyronine (T_3)	**4**	≤ 2	99.5

Hypothyrodism with:

Myxedema coma

- Life –threatening hypothyroidism.
- Serum TSH levels are high in most cases.
- ★ The **treatment of choice** is **loading dose of levothyroxine intravenously** 300-400µg initially followed by 50µg daily.
- **I.V. liothyronine** for **rapid** response but it may provoke **cardiotoxicity**.
- **I.V. hydrocortisone** may be used in case of **adrenal and pituitary insufficiency.**
- It is important to give all preparations **I.V**, because patients with myxedema coma absorb drugs poorly from other routes.

Pregnancy

❖ In pregnant hypothyroid patient **20-30% increase in thyroxine is required** because of:

1. **Elevated maternal thyroxine binding globulin** (TBG) induced by **estrogen.**

   الإستروجين العالي عند الستّ الحامل حيأثر بالسلب على الثايرود هرمونز، بيزوّد الفورميشن أف TBG ، فبيصير عندها هيبو، عشان كذا بنعطيها هورمونز أكثر.

2. Early development of **fetal brain** depends on maternal thyroxine.

Summary-1 | Anti-hyperthyroidism

1- Thioamides

Drug	Propylthiouracil (PTU)	Methimazole & Carbimazole
MOA	- Inhibit synthesis of thyroid hormones by inhibiting the peroxidase enzyme that catalyzes the iodination of tyrosine residues. - PTU: blocks the conversion of T4 to T3 in the peripheral tissues.	
P.K	- Rapidly absorbed. - Accumulate in thyroid. - Cross the placenta.	
	- 80-90% protein binding. - Short $T_{1\2}$ - Cross the placenta. - Less secreted in breast milk → Recommended in pregnancy & breast feeding.	- Most of the drug is free. - Slower excretion (48h) - Concentrated in thyroid. - Secreted in breast milk → not recommended in pregnancy & breast feeding.
ADRs	Skin reactions, Arthralgia, Polyarthritis, GIT effects, Agranulocytosis.	
	Immunoallergic hepatitis, ANCA + vasculitis.	Abnormal sense of taste or smell.

2- IODINE (Lugol's solution, potassium iodide)

Drug	- Organic iodides as: iopanoic acid or ipodate. - Potassium iodide.
MOA	- Inhibit thyroid hormone synthesis & release. - Block the peripheral conversion of T4 to T3. - The effect is not sustained (produce a temporary remission of symptoms)
Uses	- Prior to thyroid surgery to decrease vascularity & size of the gland. - Following radio-active iodine therapy - Thyrotoxicosis
C.I	- Should not be used as a single therapy - Should not be used in pregnancy. - May produce iodism (Rare, as iodine is not much used now) - Iodism Symptoms: Skin rash, hypersalivation, oral ulcers , metallic taste, bad breath.

3- Radioactive iodine (RAI)

Drug	- ^{131}I 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	- Clinical improvement may take 2-3 months. - Cross placenta & excreted in breast milk. - Available as a solution or in capsules.
Uses	- Hyperthyroidism mainly in old patients (above 40). - Graves' disease. - Patients with toxic nodular goiter. - As a diagnostic.
Disadvantages	- High incidence of delayed hypothyroidism. - Large doses have cytotoxic actions (necrosis of the follicular cells followed by fibrosis). - May cause genetic damage. - May cause leukemia & neoplasia.

4- Adrenoceptor blocking agents

Drug	Propranolol, Atenolol, Metoprolol	C.I	Asthmatic patients → in case of Propranolol.
MOA	Adjunctive therapy to relief the adrenergic symptoms of hyperthyroidism such as tremor, palpitation, heat intolerance and nervousness.		

Summary-2

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**.

Management of hyperthyroidism due to Graves' disease

Sever	Mild-moderate
- 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.	- Child, pregnant, or lactating women: start methimazole, 5–30 mg/day, (PTU preferred in pregnant women). - If treated then it relapsed → definitive radiodine therapy in adults

Anti-Hypothyrodism

Drug	Levothyroxine (T_4)
P.K	- A synthetic form of the thyroxine (T4), is the drug of choice for replacement therapy. - Stable and has a long half life (7 days) → given once daily. - Absorption is increased when hormone is given on empty stomach
Uses	- Hypothyroidism of almost all etiology.
ADRs	Over dose: - Child: Restlessness, insomnia, accelerated bone maturation. - Adult: arrhythmias, tremor, heat intolerance.
C.I	Old pts & pts w\ cardiac problems: treatment is started with reduced dosage.

	Liothyronine (T3)	Liotrix
P.K	- More potent & rapid action than levothyroxine. - Short $T_{1\backslash 2}$ → not recommended for routine replacement therapy.	- Combination of synthetic T4 & T3 in ration 4:1. - The major limitation to this product are high cost & lack of therapeutic rationale.
C.I	- Should be avoided in cardiac pts.	

Hypothyrodism with:

Myxedema coma	Pregnancy
- Life threatening hypothyrodism. - The treatment of choice is **loading dose of levothyroxin I.V** 300-400µg initially followed by 50µg daily. - I.V liothyronine for **rapid** response but it may provoke **cardiotoxicity**. - I.V hydrocortisone → may be used in case of adrenal & pituitary insufficiency.	○ In pregnant hypothyroid patient 20-30% increase in thyroxine is required because of: 1. Elevated maternal thyroxine binding globulin (**TBG**) induced by **estrogen**. 2. Early development of **fetal brain** which depends on **maternal thyroxine**.

Extra summaries

Drugs in thyroid disease

Drugs for hyperthyroidism

- *Radioiodine*, given orally, is selectively taken up by thyroid and damages cells; it emits short-range β radiation, which affects only thyroid follicle cells. Hypothyroidism will eventually occur.
- *Thioureylenes* (e.g. **carbimazole**, **propylthiouracil**) decrease the synthesis of thyroid hormones; the mechanism is through inhibition of thyroperoxidase, thus reducing iodination of thyroglobulin. They are given orally.
- *Iodine*, given orally in high doses, transiently reduces thyroid hormone secretion and decreases vascularity of the gland.

Drugs for hypothyroidism

- **Levothyroxine** has all the actions of endogenous thyroxine; it is given orally.
- **Liothyronine** has all the actions of endogenous tri-iodothyronine; it is given intravenously.

Clinical use of drugs acting on the thyroid

Radioiodine

- Hyperthyroidism (Graves' disease, multinodular toxic goitre).
- Relapse of hyperthyroidism after failed medical or surgical treatment.

Carbimazole or propylthiouracil

- Hyperthyroidism (diffuse toxic goitre); at least 1 year of treatment is needed.
- Preliminary to surgery for toxic goitre.
- Part of the treatment of *thyroid storm* (very severe hyperthyroidism); **propylthiouracil** is preferred. The β-adrenoceptor antagonists (e.g. **propranolol**) are also used.

Thyroid hormones and iodine

- **Levothyroxine** (T_4) is the standard replacement therapy for hypothyroidism.
- **Liothyronine** (T_3) is the treatment of choice for myxoedema coma.
- Iodine dissolved in aqueous potassium iodide ('**Lugol's iodine**') is used short term to control thyrotoxicosis *preoperatively*. It reduces the vascularity of the gland.

SUMMARY Drugs Used in the Management of Thyroid Disease

Class	Mechanism of Action and Effects	Indications	Pharmacokinetics, Toxicities, Interactions
Thyroid Preparations			
• Levothyroxine (T_4) • Liothyronine (T_3)	Activation of nuclear receptors results in gene expression with RNA formation and protein synthesis	Hypothyroidism	See Table 38–1• maximum effect seen after 6–8 weeks of therapy • *Toxicity:* See Table 38–4 for symptoms of thyroid excess
Antithyroid Agents			
THIOAMIDES			
• Methimazole • Propylthiouracil (PTU)	Inhibit thyroid peroxidase reactions • block iodine organification • inhibit peripheral deiodination of T_4 and T_3 (primarily PTU)	Hyperthyroidism	Oral • duration of action: 24 h (methimazole), 6–8 h (PTU) • delayed onset of action • *Toxicity:* Nausea, gastrointestinal distress, rash, agranulocytosis, hepatitis (PTU black box), hypothyroidism
IODIDES			
• Lugol solution • Potassium iodide	Inhibit organification and hormone release • reduce the size and vascularity of the gland	Preparation for surgical thyroidectomy	Oral • acute onset within 2–7 days • *Toxicity:* Rare (see text)
BETA BLOCKERS			
• Propranolol	Inhibition of β adrenoreceptors • inhibit T_4 to T_3 conversion (only propranolol)	Hyperthyroidism, especially thyroid storm • adjunct to control tachycardia, hypertension, and atrial fibrillation	Onset within hours • duration of 4–6 h (oral propranolol) • *Toxicity:* Asthma, AV blockade, hypotension, bradycardia
RADIOACTIVE IODINE ^{131}I (RAI)			
	Radiation destruction of thyroid parenchyma	Hyperthyroidism • patients should be euthyroid or on β blockers before RAI • avoid in pregnancy or in nursing mothers	Oral • half-life 5 days • onset of 6–12 weeks • maximum effect in 3–6 months • *Toxicity:* Sore throat, sialitis, hypothyroidism

MCQs

1- Patient has hyperthyroidism. After treating him he developed vasculitis (ANCA+) which one of these drugs is most likely to have side affect:
A- PTU
B- Methimazole
C- Liotrex
D- Levothyroxine

2- 30-yaer old patient has severe hyperthyroidism. To manage his case we should start treat him with:
A- Methimazole
B- Beta blockers
C- PTU
D- Radioiodine

3- 5-year old patient was diagnosed with mild hyperthyroidism.
which of these drugs should we start with:
A- PTU
B- Methimazole
C- Radioactive iodine
D- Propranolol

4- Patient who developed thyrotoxicosis he was treated with drug that caused to him hypersalivation, oral ulceration and metallic taste which of these drugs can cause such side affect :
A- Aspirin
B- Potassium iodide
C- Methimazole
D- Liotrex

5- Symptoms of hyperthyroidism include all of following except:
A- Tachycardia
B- Nervousness
C- Intolerance to cold
D- Body wasting

6- A cardiac patient was diagnosed with hypothyroidism, which drug we should avoid:
A- Levothyroxine
B- Liotrix
C- Liothyronine

7- Liotrix is a:
A- Combination of synthetic T4 & T3
B- T3
C- Synthetic form of the thyroxine(T4)

8- A patient with Myxedema Coma was diagnosed to have adrenal and pituitary insufficiency the treatment is:
A- I.V Liotrix
B- I.V. hydrocortisone
C- I.V. Liothyronine

9- A 33-year-old woman presents to her primary care physician with tachycardia, heat intolerance, tremor, and unintentional weight loss. A thyroid scan shows multiple regions of thyroid taking up excess iodine. She is prescribed with a drug that will decrease synthesis of thyroid hormones and decrease the peripheral conversion of T4 to T3. Which drug is this?
A- Levothyroxine
B- Methimazole
C- Propylthiouracil

10- The following thyroid inhibitor does not produce goiter when given in over dose:
A- Propylthiouracil
B- Carbimazole
C- Sodium thiocyanate
D- Radioactive iodine

11- Carbimazole acts by inhibiting:
A- Iodide trapping
B- Oxidation of iodide
C- Proteolysis of thyroglobulin
D- Synthesis of thyroglobulin protein

Answers: 1-A 2-D 3-B 4-B 5-C 6-C 7-A 8-B 9-C 10-D 11-B

Thank you for checking our team!

Pharmacology 435

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Sources:

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