



Endocrine  
System

**PHARMACOLOGY**  
432 TEAM



# DRUGS USED IN HYPERTHYROIDISM AND HYPOTHYROIDISM

## Learning Objectives:

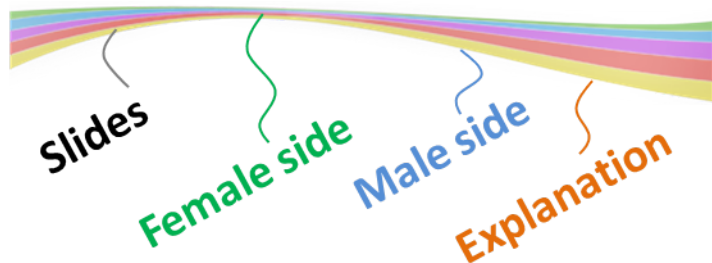
1. Classify common drugs used for treatment of hyperthyroidism
2. Details the drugs regarding , mechanism of action , pharmacological effects , clinical uses & side effects
3. Recognize treatment of special cases of hyperthyroidism such as pregnancy, breast feeding , Grave,s disease & thyroid storm
4. 1.Classify common drugs used for treatment of hypothyroidism
5. 2.Details the drugs regarding , mechanism of action , pharmacological effects , clinical uses & side effects
6. 3.Recognize treatment of special cases of hypothyroidism .

This lecture was done by:

Alanoud alhoqail & Heba alsharif  
Dana Al-Olyet & Raghad Al-mutlaq

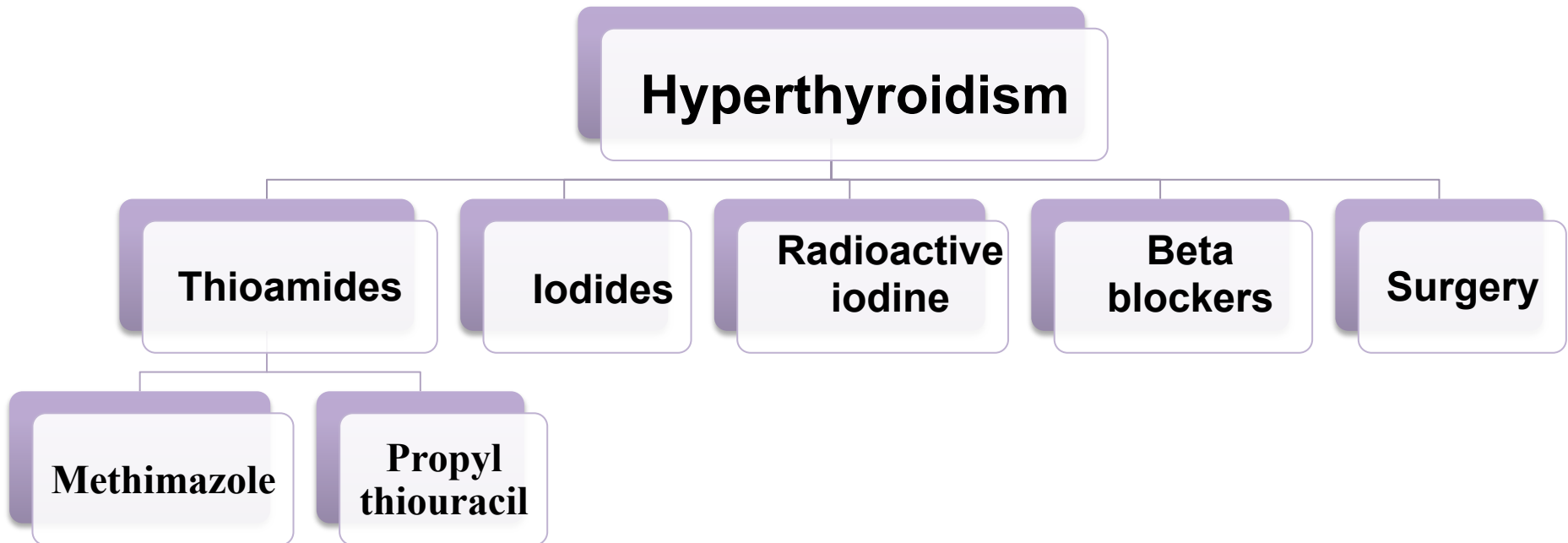
And reviewed by:

Abdullah AL-Anazi & Mohammed Abalkhail





# Mind Map

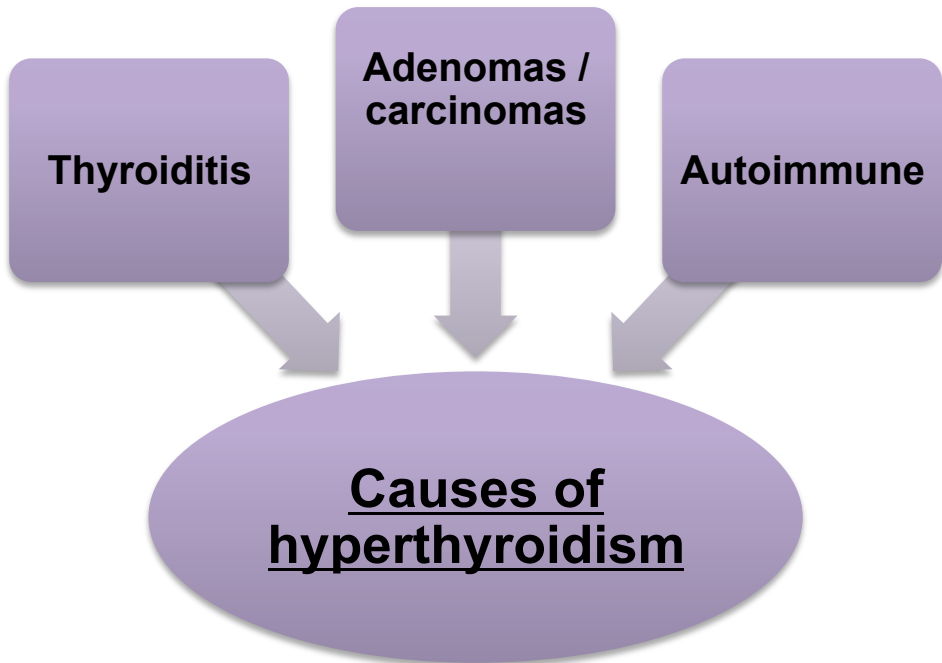




# Hyperthyroidism

**Elevated levels of  $T_3$  and  $T_4$  in the blood.**

## Manifestations of Hyperthyroidism



- Nervousness, irritability.
- Tremors
- Palpitation
- Weight loss
- Sweating
- Heat intolerance
- Diarrhea
- short breath
- Itching
- Xophthalmos
- Thyroid Enlargement

In the late stage of the disease if it is untreated



## Grave's disease

**Most common cause of hyperthyroidism  
60-80%**

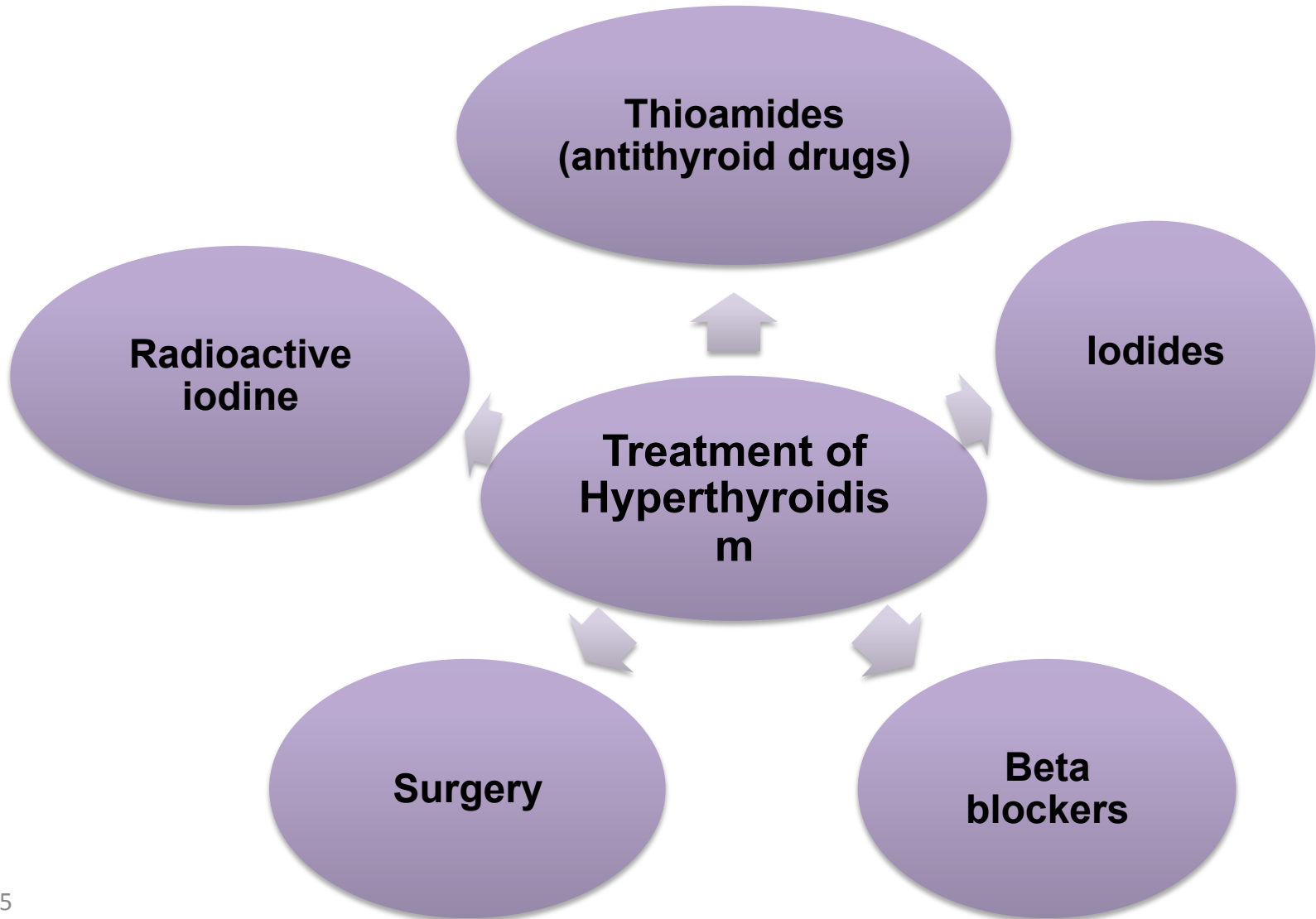
**Autoimmune disorder**

**High levels of circulating immunoglobulins .**

**immunoglobulins bind to and stimulate the thyrotropin ( TSH)  
receptor , resulting in sustained thyroid over activity & it can be  
familial**



# Treatment of Hyperthyroidism



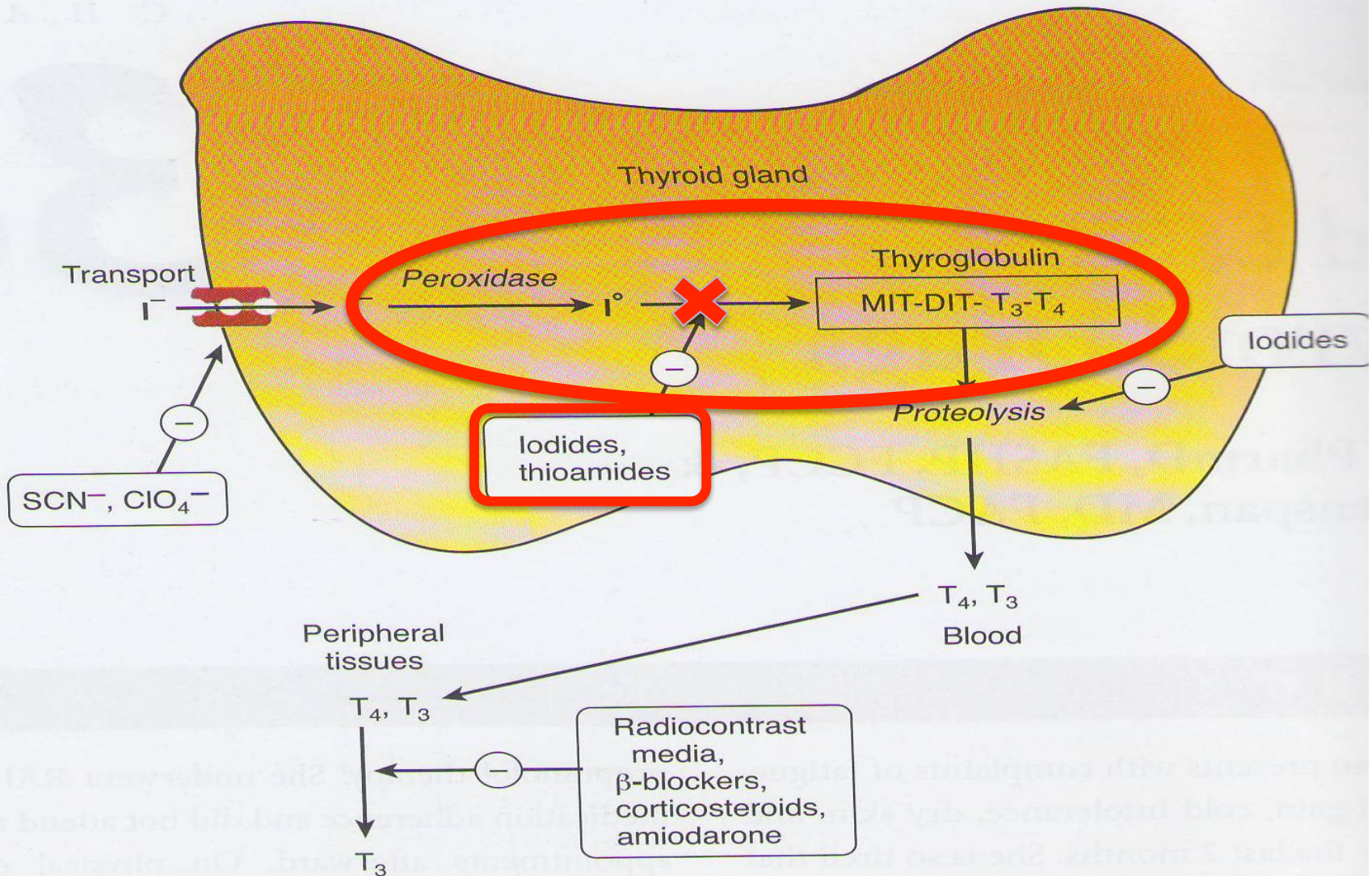


**Two types :** 1) Methimazole 2) Propyl thiouracil

## Mechanism of action

- **Inhibit synthesis of thyroid hormones**
- By inhibiting **peroxidase enzyme** that catalyzes:
  - 1)iodination of tyrosine residues in the thyroglobulin
  - 2)coupling iodotyrosines to form T3 & T4.

- They block the **conversion of T4 to T3** within the thyroid & in peripheral tissues.



Biosynthesis of thyroid hormones. The sites of action of various drugs that interfere with thyroid hormone



	<b>Propylthiouracil</b>	<b>Methimazole</b>
<b>Absorption</b>	Rapidly absorbed from GIT	Rapidly absorbed from GIT
<b>Protein binding</b>	Bound to the plasma proteins 80-90%	Most of the drug is free
<b>accumulation</b>	accumulated in thyroid	accumulated in thyroid
<b>Excretion</b>	Kidneys as inactive metabolite within 24 hrs Rapid excretion	Excretion slow, 60-70% of drug is recovered in urine in 48 hrs Slow excretion
<b>Half life</b>	1.5 hrs ( short half-life)	6 hrs ( long half-life)
<b>Administration</b>	Every 6-8 hrs (more than one dose per a day due to the short half life of the drug )	As a single dose





	<b>Propylthiouracil</b>	<b>Methimazole</b>
<b>Pregnancy</b>	<ul style="list-style-type: none"> <li>• cross placenta &amp; Concentrate in fetal thyroid.</li> <li>• <b>as it is highly protein bound ,crossing placenta is less readily and in low quantity so &gt;&gt; recommended in pregnancy.</b></li> </ul>	<ul style="list-style-type: none"> <li>• cross placenta &amp; Concentrate in fetal thyroid.</li> </ul> <p>(Because it is found in the free form in the blood, so it can easily cross the placental barrier)</p> <p><b>Not recommended in pregnancy.</b></p>
<b>Breastfeeding</b>	<p>Less secreted in breast milk <b>Recommended</b></p>	<p>secreted <b>Not recommended</b></p>



## Adverse Effects:

- Cutaneous reactions ( urticaria ,maculopapular rash )
- Arthralgia
- GI upset , **Hepatotoxicity ( mainly with methimazole)**
- **Most dangerous complication is agranulocytosis (severe neutropenia) occur within 90 days of treatment. (so periodic white blood cell count should be done regularly)**

**Notes:** Clinically methimazole is preferred in ER conditions as thyrotoxicosis because it's rapidly acting

In usual cases>> propylthiouracil is preferred because methimazole causes hepatotoxicity



Mechanism of action	Clinical uses	<u>Precautions / toxicity:</u>
<ul style="list-style-type: none"> <li>Inhibit thyroid hormone synthesis and release</li> <li>Block the peripheral conversion of T4 to T3 .</li> <li>The effect is not sustained ( <b>produce a temporary remission of symptoms</b> )</li> </ul> <p>&gt;&gt;used in the short term treatment . For ex. Before the thyroid surgery</p> <div data-bbox="54 999 602 1313" style="border: 1px solid gray; border-radius: 15px; padding: 10px; margin-top: 20px;"> <p>Remember :Walf Chickoff effect: excessive iodine intake &gt;&gt; temporary inactivation of peroxidase</p> </div>	<ul style="list-style-type: none"> <li>Prior to thyroid surgery to decrease vascularity &amp; size of the gland .</li> <li>Following radio active iodine therapy.</li> <li>Thyrotoxicosis</li> </ul> <p>Examples :(difference between the formulas is the concentration of iodide )</p> <ul style="list-style-type: none"> <li>Organic iodides as :iopanoic acid or ipodate</li> <li>Potassium iodide</li> </ul> <div data-bbox="710 1106 1255 1320" style="border: 1px solid gray; border-radius: 15px; padding: 10px; margin-top: 20px;"> <p>Iodides+Methomazole &gt;&gt; in thyrotoxicosis (ER) for rapid remission of clinical manifestations</p> </div>	<ul style="list-style-type: none"> <li>Should not be used as a single therapy</li> <li><b>Should not be used in pregnancy</b> (cause teratogenicity)</li> <li>May produce iodism (acniform rash, swelling of salivary glands, mucous membrane ulceration, metallic taste bleeding disorders and rarely anaphylaxis).</li> </ul>



**<sup>131</sup>I isotope ( therapeutic effect due to emission of β rays )**

Mechanism of action	Half life	Pregnancy & breastfeeding	Administraction	Clinical uses	Adverse effects
<p>Accumulates in the thyroid gland and <b>destroys parenchymal cells</b>, producing a long-term decrease in thyroid hormone levels.                      Clinical <b>improvement may take 2-3 months</b></p>	<p>5 days</p>	<p>Cross placenta &amp; excreted in breast milk</p> <p><b>#in pregnancy and nursing mom</b></p>	<p>Easy to administer , effective , painless and less expensive</p> <p>Available as a solution or in capsules.</p>	<ul style="list-style-type: none"> <li>❖ <b>Hyperthyroidism mainly in old patients(above 40) because it may cause genetic damage and infertility</b></li> <li>❖ <b>Graves' disease</b></li> <li>❖ Patients with toxic nodular goiter</li> <li>❖ As a diagnostic</li> </ul>	<p><b>High incidence of delayed hypothyroidism</b></p> <p>Large doses have cytotoxic actions ( necrosis of the follicular cells followed by fibrosis )</p> <p>May cause genetic damage</p> <p>May cause leukemia &amp; neoplasia (carcinogenic )</p>



## ADRENOCEPTOR BLOCKING AGENTS:

### Beta-blockers

- **Adjunctive therapy** to relief the adrenergic symptoms of hyperthyroidism such as tremor, palpitation, heat intolerance and nervousness.
- E.g. Propranolol, Atenolol , Metoprolol.
- **Propranolol is contraindicated in asthmatic patients** (because it is not selective causing bronchospasm in asthmatic patients )

## Surgical treatment

### THYROIDECTOMY :

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



## THYROID STORM

### Thyrotoxicosis during pregnancy

## 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.

**Is a medical emergency .**

### Treatment :

**Propranolol** 1-2mg slows IV or 40-80 mg orally every 6 hours.

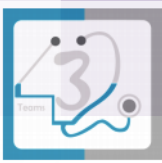
**Potassium iodide** 10 drops orally daily or  
**Propylthiouracil** 250 mg orally every six hours or 400 mg every six hours rectally.

**Hydrocortisone** 50 mg IV every 6 hours to prevent shock.

If above methods fail  
**peritoneal dialysis.**

### Thyrotoxicosis during pregnancy

- **Better to start therapy before pregnancy** with  $^{131}\text{I}$  or subtotal thyroidectomy to avoid acute exacerbation during pregnancy
- **During pregnancy radioiodine is contraindicated.**
- **Propylthiouracil is the drug of choice during pregnancy. (give the least therapeutic dose)**



Treatment of hypothyroidism  
(replacement therapy of thyroid hormone) .

**Levothyroxine: (T<sub>4</sub>)**

Used clinically in all cases .

Start with small dose  
and increase it  
gradually with old  
and cardiac patient .

**Liothyronine:  
(T<sub>3</sub>)**

contraindicated in  
**cardiac patient.**



## Hypothyroidism

**Thyroid gland does not produce enough hormones**

- **Congenital ( cretinism , dwarfism)>> you should start treatment**
- **Autoimmune disorder ( Hashimotos thyroiditis)**
- **Irradiation**
- **Surgical removal of thyroid gland**
- **Thyroid carcinoma**

**People who are most at risk include those over age 50 & mainly in females & Diagnosed by low plasma levels of T3 & T4.**

**Manifestations of Hypothyroidism :**

**Fatigue and lack of energy , weight gain , Dry and cold skin ,Dry hairs , Constipation , Slowed thinking , Bradycardia, Heavy menses .**





<u>Levothyroxie(t<sub>4</sub>)</u>	Clinical Uses	Adverse Effects Of <u>Over Doses</u>	Adverse Effects Of <u>Under-dosing</u>
<ol style="list-style-type: none"> <li>1. A synthetic form of the thyroxine (T<sub>4</sub>) .</li> <li>2. <b>The drug of choice for replacement therapy.</b></li> <li>3. Stable and has a long half life ( 7 days).</li> <li>4. Administered once daily.</li> <li>5. Oral(0.025-0.3mg) &amp; parental(200-500 µg) preparations.</li> <li>6. Absorption is increased when it is given on empty stomach.</li> </ol>	<ol style="list-style-type: none"> <li>1. Hypothyroidism, regardless of etiology including : congenital ,Autoimmune (Hashimotothyroiditis), Pregnancy ,Thyroid carcinoma.</li> <li>2. <b>In old patients and cardiac patients, treatment is started with reduced dosage then increased gradually.</b></li> <li>3. Restore normal thyroid levels within 2-3 weeks.</li> <li>4. levothyroxine is given in a dose of 12.5 – 25 µg/day for two weeks and then increasing it after every two weeks.</li> </ol> <p style="color: green;">Give full therapeutic dose to young healthy patient</p>	<p><b>CHILDREN :</b> Restlessness, insomnia, accelerated bone maturation.</p> <p><b>ADULTS :</b> Tachycardia, palpitation, cardiac arrhythmias, tremor , restlessness , heat intolerance , headache, muscle pain Change in appetite, diarrhea, weight loss.</p> <p style="color: orange;">(hyperthyroidism manifestations)</p>	<ol style="list-style-type: none"> <li>1. <b>Sluggishness.</b></li> <li>2. <b>Mental dullness.</b></li> <li>3. <b>Feeling cold.</b></li> <li>4. <b>Muscle cramps.</b></li> <li>5. <b>Slow motion.</b></li> </ol> <p style="color: orange;">Over hypothyroidism Manifestations &amp; patients will complain that the symptoms are deteriorating.)</p>



Drug	Liothyronine T3	Liotrix
Features	<p><b>More potent (3-4) times</b>  <b>Rapid action</b>  <b>Short half life</b> (multiple doses daily)+not recommended for routine replacement therapy</p>	<p>Combination of T4 and T3 in a ratio 4:1 that attempt to mimic the natural hormonal secretion</p>
Uses	<p>Short term suppression of TSH                  Given orally(5-50) or parenteral(10)                  Should <b>NOT</b> be given to a <b>cardiac patient</b></p>	<p>limitations to this product are high cost &amp; lack of therapeutic rationale (because that T4 turns to T3 peripherally)</p>

## Myxedema coma

**Myxedema coma** : life threatening hypothyroidism  
 +end stage of untreated hypothyroidism

**Treatment of choice:** loading dose of **I.V levothyroxine** 300-400µg initially followed by 50µg **daily**

**Another treatment line:** I.V Liothyronine for rapid response but it may provoke **cardio-toxicity**

\* I.V hydrocortisone may be used in case of adrenal and pituitary insufficiency (**shock**)

## Hypothyroidism and pregnancy

In pregnant hypothyroid patient 20-30 % increase in thyroxin is required because:

- Maternal TBG is elevated by estrogen
- Early development of fetal brain which depends on maternal thyroxine (prophylaxis)
- **Levothyroxine is the drug of choice but dose should be increased little**



# Summary

- The Propylthiouracil has short duration of action, but Methimazole has longer duration of action.
- The propylthiouracil is most recommended in the pregnant and breast feeding women .
- **Most dangerous complication is agranulocytosis of thioamides .**
- The iodide produces a temporary remission of symptoms of the hyperthyroidism so it is used before surgery .
- Radioactive iodine destroys parenchymal cells.
- Beta-blockers are adjunctive therapy to relieve the adrenergic symptoms of hyperthyroidism such as tremor, palpitation, heat intolerance and nervousness.
- Thyroid storm is a sudden **acute exacerbation** of all of the symptoms of thyrotoxicosis, presenting as a life threatening syndrome.



1. **Question: what is the drug of choice for treating hyperthyroidism in pregnant women ?**
  - A. Propylthiouracil
  - B. Methimazole
  - C. Iodide
  
2. **Question: in emergency cases of hyperthyroidism we give?**
  - A. propylthiouracil
  - B. Methiomazole
  
3. **Question: the following drug is not given in asthmatic patients?**
  - A. propranolol
  - B. Atenolol
  - C. Metoprolol
  
4. **Question: inhibition of peroxidase enzyme is the mechanism of action of:**
  - A. Propylthiouracil
  - B. Methimazole
  - C. both
  
5. **Question: hepatotoxicity mainly side effect of:**
  - A. propylthiouracil
  - B. Methiomazole
  - C. iodide

Answers: 1-A , 2-B ,3-A , : 4-C , 5-B



**6- endocrinologist described a low dose (mistake dose) of LEVOTHYROXINE (T4) to a hypothyroidism patient for 2 weeks, then the patient came back complaining from muscle cramps and slow motion. Which drug is responsible for that?**

- A. Liotrix
- B. B blockers
- C. levothyroxine

**7- Which one of these patient you have to take precaution, when you give levothyroxine**

- A. Cardiac and old patient
- B. Young and children
- C. Pregnant women

**8- Which one of the following is the first line treatment for hypothyroidism?**

- A. Liotrix
- B. Levothyroxine
- C.  $\beta$  blockers
- D. Liothyronine

**9- What are the risk factors of leaving a pregnant women suffering from hypothyroidism without treatment?**

- A. Genetic mutations
- B. Miscarriage
- C. Fetal CNS problems



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**Pharmacology Leaders**

**Tuqa Al-Kaff & Abdullah Al-Anzi**

**Pharmacologyteam1@gmail.com**