


**EMORY**  
HEALTHCARE

## Review of Thyroid Disorders



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### Disclosures

- I do not have a relevant financial relationship with any corporate organization offering financial support or grant monies for this continuing education activity, or any affiliation with an organization whose philosophy could potentially bias my presentation.
- The following investigators have nothing to disclose:
  - Kyle W Furlow, PharmD, MHIIM
  - Heidi King Berman, PharmD, BCPS

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### Objectives

Pharmacists:

1. Discuss the pathophysiology of hypothyroidism and hyperthyroidism
2. Identify appropriate treatment options for hypothyroidism and hyperthyroidism
3. Recognize the presentation and management of thyroid storm and myxedema coma

Pharmacy Technicians:

1. List risk factors and causes of thyroid disorders including special populations
2. Outline common medications utilized for hypothyroidism and hyperthyroidism
3. Review the medical emergencies that can occur with thyroid disorders

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### Patient Case - DD

DD is a 71-year-old female with a past medical history of T2DM, HTN, and a multinodular thyroid goiter (dx biopsy 2018) who presented to the ED after a fall in the setting of four weeks of progressive generalized weakness, weight loss, and decreased appetite.

- Home medications (noncompliant)
  - Sitagliptin 100 mg PO daily
  - Bisoprolol/HCTZ 5/6.25 mg PO daily
  - Losartan 25 mg PO daily
  - Glimepiride 2 mg PO daily



T2DM=Type 2 Diabetes Mellitus | HTN=Hypertension | dx=Diagnostic | ED=Emergency Department | HCTZ=Hydrochlorothiazide

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### Vitals and Labs

- Vitals: BP = 181/81 mmHg, HR = 119 bpm, Resp=16 br/min
- Additional Labs:
  - PTH: 11 pg/mL ↓
  - HgbA1C: 9.4 % ↑
- Liver Enzymes:
  - AlkPhos: 134 u/L ↑
  - ALT: 60 u/L ↑
  - AST: 66 u/L ↑

| Thyroid Function Tests                       |                                 |
|--|---------------------------------|
| Thyroxine free (T <sub>4</sub> Total)        | 2.78 ng/dL ↑<br>(14.0 mcg/dL) ↑ |
| Triiodothyronine free (T <sub>3</sub> Total) | 8.7 pg/dL ↑<br>(216 ng/dL) ↑    |
| TSH  | < 0.01 mIU/mL ↓                 |
| TSH receptor Ab                              | > 40.00 IU/L ↑                  |
| TSI  | > 40.00 IU/L ↑                  |

|     |    |      |     |
|-----|----|------|-----|
| 136 | 95 | 29   | 288 |
| 3.0 | 25 | 0.41 |     |

BP=Blood Pressure | HR=Heart Rate | Resp=Respiratory Rate | PTH=Parathyroid Hormone | HgbA1C=Hemoglobin A1C | TSH=Thyroid Stimulating Hormone | TSI=Thyroid Stimulating Immunoglobulin | AlkPhos=Alkaline Phosphatase | ALT=Alanine Aminotransferase | AST=Aspartate Aminotransferase

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### To be continued . . .




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### Hypothyroidism Background

- Worldwide iodine deficiency remains the foremost cause of hypothyroidism
- In the US and other areas; autoimmune thyroid disease (Hashimoto disease) is the most common cause
- Primary process: thyroid gland is insufficient
- Secondary process: pituitary hormone deficiencies
- Tertiary process: hypothalamus insufficiencies

Gallonde DY, Rowley KD, Sweeney LB. Hypothyroidism: an update. Am Fam Physician. 2012;86(3):244-251. Accessed December 9, 2020

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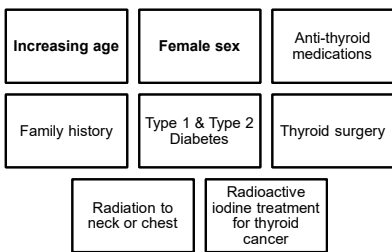
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### Risk Factors - Hypothyroidism



Gallonde DY, Rowley KD, Sweeney LB. Hypothyroidism: an update. Am Fam Physician. 2012;86(3):244-251. Accessed December 9, 2020

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### Hyperthyroidism Background

Thyroid hormones play a major role to maintain metabolic stability

Hyperthyroidism is when the thyroid gland increases hormone production and secretion in excess

Thyrotoxicosis is the clinical syndrome of excess thyroid hormones circulating in the blood and exposed to tissue

Prevalence is about 1.3% in the USA

De Leo S, Lee SY, Braverman LE. Hyperthyroidism. Lancet. 2016;388(10047):906-918. Mathew P, Rawla P. Hyperthyroidism. In: StatPearls [Internet]. StatPearls Publishing.

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### Risk Factors - Hyperthyroidism

|                               |  |  |
|-------------------------------|--|--|
| Increasing age                | Female sex   | Large intake of iodine via food or medications |
| Family history                | Pernicious Anemia (Vitamin B <sub>12</sub> deficiency) | Type 1 & Type 2 Diabetes                       |
| Primary adrenal insufficiency | Recent Pregnancy                                       | Smoking  |

De Leo S, Lee SY, Braverman LE. Hyperthyroidism. Lancet. 2016;388(10047):906-918.  
 Mathew P, Rana P. Hyperthyroidism. In: StatPearls [Internet]. StatPearls Publishing; 2022.  
 Sawicka-Gutaj N, Gutaj P, Sowiński J, et al. Influence of cigarette smoking on thyroid gland—an update. Endokrynologia Polska. 2014;65(1):54-62.

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### Thyroid Hormones

#### Pathophysiology

- Hypothalamus
  - Releases TRH
- Anterior Pituitary
  - Produces TSH
- TSH binds TSH-R
  - Thyroglobulin
  - Stimulate TPO
- Thyroid Hormones
  - T<sub>4</sub> >> T<sub>3</sub> synthesized

TRH=Thyroid Releasing Hormone | TSH=Thyroid Stimulating Hormone | T<sub>3</sub>=Triiodothyronine | T<sub>4</sub>=Thyroxine  
 TPO=Thyroid Peroxidase | Image retrieved from: Cleveland Clinic  
 De Leo S, Lee SY, Braverman LE. Hyperthyroidism. Lancet. 2016;388(10047):906-918. doi:10.1016/S0140-6736(16)0278-6  
 DiPiro JT, Talbert RL, Yee GC, Matzke GR, Wells BG, Posey L, eds. Pharmacotherapy: A Pathophysiologic Approach. 10e. McGraw Hill; 2017.

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Regulation of thyroid hormone starts at the hypothalamus

TRH released into the hypothalamic-hypophyseal portal system within the anterior pituitary gland

TRH stimulates thyrotropin cells which release TSH

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### Pathophysiology

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  - Stimulate TPO
- Thyroid Hormones
  - $T_4 \gg T_3$  synthesized

TSH triggers the thyroid to produce  $T_4$  and  $T_3$   
 The thyroid also needs adequate amounts of iodine, to create  $T_4$  and  $T_3$   
 Hormones released: 80% is  $T_4$  and 20% is  $T_3$

TRH=Thyroid Releasing Hormone | TSH=Thyroid Stimulating Hormone |  $T_3$ =Triiodothyronine |  $T_4$ =Thyroxine | TPO=Thyroid Peroxidase | Image retrieved from: Cleveland Clinic; De Leo S, Lee SY, Braverman LE. Hyperthyroidism. Lancet. 2016;388(10047):906-918. doi:10.1016/S0140-6736(16)00278-6; DiPiro JT, Talbert RL, Yee GC, Matzke GR, Wells BG, Posey L, eds. Pharmacotherapy: A Pathophysiologic Approach, 10e. McGraw Hill; 2017.

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### Hypothalamic-Pituitary-Thyroid Axis Negative Feedback

- Feedback loop system:
  - Hypothalamus
  - Pituitary gland
  - Thyroid gland
- When levels of  $T_3$  and  $T_4$  decrease below normal, the hypothalamus releases thyroid regulating hormone (TRH)

TRH=Thyroid Releasing Hormone | TSH=Thyroid Stimulating Hormone |  $T_3$ =Triiodothyronine |  $T_4$ =Thyroxine | DiPiro JT, Talbert RL, Yee GC, Matzke GR, Wells BG, Posey L, eds. Pharmacotherapy: A Pathophysiologic Approach, 10e. McGraw Hill; 2017.

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### Diagnosis – Hypothyroidism

- Signs and Symptoms of hypothyroidism
- Thyroid Studies
  - Elevated TSH
    - Low T<sub>4</sub> or normal and Low FT<sub>4</sub>
- Subclinical versus primary hypothyroidism
  - Subclinical defined by normal FT<sub>4</sub> levels only
  - Treat as hypothyroidism if:
    - TSH > 10 mIU/L
    - Elevated TPO antibody ~ Hashimoto thyroiditis
- ATA and AACE recommend starting levothyroxine or endocrinology referral especially if pregnant (9 doses/week)

TSH=Thyroid Stimulating Hormone | ATA=American Thyroid Association | AACE=American Association of Clinical Endocrinologists  
 Gallonde DV, Rowley KD, Sweeney LB. Hypothyroidism: an update. Am Fam Physician. 2012;86(3):244-251. Accessed December 9, 2020.

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### Diagnosis – Hyperthyroidism

- Signs and Symptoms of hyperthyroidism
- Thyroid Studies
  - Elevated T<sub>4</sub>
  - Suppressed TSH
- Subclinical versus overt hyperthyroidism
  - Subclinical defined by the abnormal TSH levels only
- ATA and AACE recommend a thyroid radioactive iodine uptake test

TSH=Thyroid Stimulating Hormone | ATA=American Thyroid Association | AACE=American Association of Clinical Endocrinologists

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### Thyroid Function Testing

| Lab test                                 | Normal Range         | Hyperthyroidism | Hypothyroidism |
|--|----------------------|-----------------|----------------|
| TSH                                      | [0.45 – 5.33] mIU/mL | ?               | ?              |
| T4                                       | [5.0 – 9.8] mcg/dL   |                 |                |
| T3                                       | [87 – 178] ng/dL     |                 |                |
| T4, Free (Thyroxine)                     | [0.58 – 1.64] ng/dL  |                 |                |
| T3, Free (Triiodothyronine)              | [2.5 – 4.3] pg/mL    |                 |                |
| TSH Receptor Antibody                    | ≤ 1.75 IU/L          |                 |                |
| Thyroid Stimulating Immunoglobulin – TSI | ≤ 0.54 IU/L          |                 |                |

**Medications that interfere with Thyroid Function Testing**

- Estrogens: increases the level of binding proteins
- Biotin: false normotensive requires a 48 hours period

TRH=Thyroid Releasing Hormone | TSH=Thyroid Stimulating Hormone | T3=Triiodothyronine | T4=Thyroxine  
Kravets I. Hyperthyroidism: Diagnosis and Treatment. Am Fam Physician. 2016;93(5):363-370.

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### Thyroid Function Testing

| Lab test                                 | Normal Range         | Hyperthyroidism | Hypothyroidism |
|--|----------------------|-----------------|----------------|
| TSH                                      | [0.45 – 5.33] mIU/mL | LOW             | HIGH           |
| T4                                       | [5.0 – 9.8] mcg/dL   | HIGH            | LOW            |
| T3                                       | [87 – 178] ng/dL     | HIGH            | NORMAL         |
| T4, Free (Thyroxine)                     | [0.58 – 1.64] ng/dL  | HIGH            | LOW            |
| T3, Free (Triiodothyronine)              | [2.5 – 4.3] pg/mL    | HIGH            | NOT INDICATED  |
| TSH Receptor Antibody                    | ≤ 1.75 IU/L          | HIGH            | NOT INDICATED  |
| Thyroid Stimulating Immunoglobulin – TSI | ≤ 0.54 IU/L          | HIGH            | NOT INDICATED  |

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### Audience Participation



Which of the DD's labs would make you concerned for hyperthyroidism if it was clinically low?

- A. Thyroxine free
- B. Triiodothyronine free
- C. Thyroid Stimulating Hormone
- D. TSH receptor Ab
- E. Thyroid Stimulating Immunoglobulin

| Thyroid Function Tests           |                          |
|----------------------------------|--------------------------|
| Thyroxine free (T4 Total)        | 2.78 ng/dL (14.0 mcg/dL) |
| Triiodothyronine free (T3 Total) | 8.7 pg/dL (216 ng/dL)    |
| TSH                              | < 0.01 mIU/mL            |
| TSH receptor Ab                  | > 40.00 IU/L             |
| TSI                              | > 40.00 IU/L             |

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Which of the DD's labs would make you concerned for hyperthyroidism if it was clinically low?

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| TSI                              | > 40.00 IU/L             |

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**Hypothyroidism**

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**Signs/Symptoms of Hypothyroidism**

- Cold intolerance
- Cold sensitivity
- Dry skin
- Fatigue
- Muscle cramps
- Voice changes
- Constipation
- Weight gain
- Goiter (low iodine intake)
- Myalgias
- Weakness
- Depression
- Bradycardia
- Coarse hair or loss
- Menorrhagia
- Memory/mental impairment

Gallardo DY, Rowley KD, Saareney LB. Hypothyroidism: an update. Am Fam Physician. 2012;86(3):244-251. Accessed December 9, 2020.

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### Drugs/Conditions That Can Cause Hypothyroidism

- Interferons
- Tyrosine Kinase Inhibitors
- Amiodarone
- Lithium
- Carbamazepine
- Oxcarbazepine
- Eslicarbazepine
- Phenytoin
- Hashimoto's disease
- Iodine deficiency
- Pituitary failure
- Surgical removal of gland
- Congenital
- Ablation with radioactive iodine

Galtonde DY, Rowley KD, Sweeney LB. Hypothyroidism: an update. Am Fam Physician. 2012;86(3):244-251. Accessed December 9, 2020

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### Hypothyroidism

- Typically start with levothyroxine 1.5 - 1.8 mcg/kg/day
  - Retest TSH in 6 – 8 weeks, adjust by 12.5 - 25 mcg
- If patients are greater than > 60 years of age or known heart disease
  - Start levothyroxine 12.5 - 50 mcg/day
  - Increase dose by 25 mcg every 3 – 4 weeks until TSH is normal
- Mental change, hypothermia, stupor?
  - Consider myxedema coma! admit to ICU

Galtonde DY, Rowley KD, Sweeney LB. Hypothyroidism: an update. Am Fam Physician. 2012;86(3):244-251. Accessed December 9, 2020

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### Hypothyroidism Treatment

| Drug   | Dosing   |
|--|--|
| <b>Levothyroxine (T4)</b><br>Capsule, tablet, injection, oral solution<br><span style="border: 1px solid black; padding: 2px;">Drug of Choice</span> | Full replacement dose = 1.6 mcg/kg/day (IBW)<br>Start with full replacement dose in otherwise healthy, young (<50 years of age) patients<br>Start with partial replacement dose in milder hypothyroidism and with comorbidities - If known CAD, start with 12.5-25 mcg daily<br>Elderly patients often need 20-25% less per kg; may require < 1 mcg/kg/day |
| <b>Thyroid, Desiccated USP (T3 and T4)</b><br>Tablet   | Start 15-30 mg daily (15 mg in cardiac disease); titrate in 15 mg increments<br>Usual dose is 60-120 mg daily<br>*Natural porcine-derived thyroid that contains both T3 and T4; less predictable potency and stability*  |
| <b>Liothyronine (T3)</b><br>Tablet, injection  | Start 25 mcg daily, titrate in 12.5-25 mcg increments<br>Usual dose is 25-75 mcg daily<br>*Shorter half-life causes fluctuations in T3 levels*   |
| <b>Liotalix (T3 + T4; 1:4 ratio)</b><br>Tablet   | Start 25 mcg levothyroxine/6.25 mcg liothyronine daily<br>Usual dose: 50-100 mcg levothyroxine/12.5-25 mcg liothyronine  |

Lexicomp Online. Lexi-Drugs Online. Hudson, Ohio: Wolters Kluwer Clinical Drug Information, Inc.  
Galtonde DY, Rowley KD, Sweeney LB. Hypothyroidism: an update. Am Fam Physician. 2012;86(3):244-251. Accessed December 9, 2020

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### Hypothyroidism Treatment

**Boxed Warning:** ineffective and potentially toxic when used for obesity or weight reduction, especially in euthyroid patients; high doses can cause serious, life-threatening toxic effects!

**Contraindications:** Uncorrected adrenal insufficiency

**Warnings:** decrease dose in cardiovascular disease (chronic hypothyroidism predisposes to coronary artery disease); decrease bone mineral density which can lead to osteoporosis

**Side Effects:** hyperthyroid symptoms can occur when the dose is too high: increased HR, palpitations, sweating, weight loss, arrhythmias, irritability

**Monitoring:** TSH levels and clinical symptoms every 4-6 weeks until levels are normal, then 4-6 months later, then yearly; serum FT4 in select patients

**Notes:** highly protein bound (>99%), dose reduction may be necessary as the patient ages

**Levothyroxine PO:** should be taken with water at the same time each day for consistent absorption, at least 60 minutes before breakfast or at bedtime (at least three hours after the last meal), levothyroxine tablet colors are standard; they do not change between manufacturers

**Levothyroxine IV:** IV to PO ratio is 0.75:1

Lexicomp Online. Lexi-Drugs Online, Hudson, Ohio: Wolters Kluwer Clinical Drug Information, Inc.  
Galtonde DY, Rowley KD, Sweeney LB. Hypothyroidism: an update. Am Fam Physician. 2012;86(3):244-251. Accessed December 9, 2020.

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### Medications That Decrease Levothyroxine Absorption

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|--|--|
| <b>Medications – when these are required, they should be ingested four hours before or after levothyroxine</b> |  |
| Calcium carbonate  | Ferrous sulfate  |
| <b>Ion exchange resins</b><br>- Sodium Polystyrene sulfonate<br>- Sevelamer (Renvela)                          | Orlistat (Xenical)   |
| <b>Bile acid sequestrants</b><br>- Colesevelam (Welchol)<br>- Cholestyramine (Questran)<br>- Colestipol        | <b>Intragastric pH elevation</b><br>- Antacids (aluminum, magnesium)<br>- Proton pump inhibitors<br>- Simethicone<br>- Sucralfate (Carafate) |

Galtonde DY, Rowley KD, Sweeney LB. Hypothyroidism: an update. Am Fam Physician. 2012;86(3):244-251. Accessed December 9, 2020.

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### Levothyroxine Tablet Colors

|                     |                       |                    |                        |
|---------------------|-----------------------|--------------------|------------------------|
| 25 mcg<br>(Peach)   | 50 mcg<br>(White)     | 75 mcg<br>(Purple) | 88 mcg<br>(Olive)      |
| 100 mcg<br>(Yellow) | 112 mcg<br>(Rose)     | 125 mcg<br>(Brown) | 137 mcg<br>(Turquoise) |
| 150 mcg<br>(Blue)   | 175 mcg<br>(Lavender) | 200 mcg<br>(Pink)  | 300 mcg<br>(Green)     |

Galtonde DY, Rowley KD, Sweeney LB. Hypothyroidism: an update. Am Fam Physician. 2012;86(3):244-251. Accessed December 9, 2020.

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**Audience Participation** 

Your patient comes to the pharmacy asking the following question "I have been taking my old white levothyroxine tablets but the new bottle you gave me say 125 mcg and not the same color. What were the two prescriptions?"

- A. White; 50 mcg and 125 mcg; Brown
- B. White; 125 mcg and 125 mcg; White from a different manufacturer
- C. White; 150 mcg and 125 mcg; Blue
- D. White; 25 mcg and 125 mcg; Black

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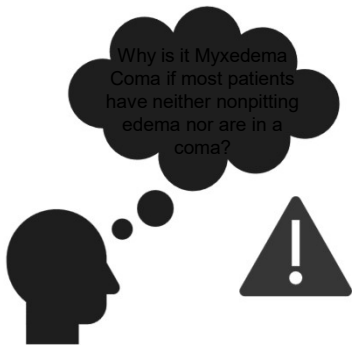
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Why is it Myxedema Coma if most patients have neither nonpitting edema nor are in a coma?

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### Myxedema Coma

- Cardinal manifestation: deterioration of mental status
- Precipitating event: lack of thyroid replacement, infection or medications
- Physical Findings: AMS, edema, hypothermia, and HTN
  - *Myxedematous face*: swelling, macroglossia, ptosis, periorbital edema, and coarse sparse hair (alopecia)
- Diagnostic: elevated CPK, SCr, and transaminases, hypoxia, hypercapnia, hypoglycemia, hyponatremia, and leukopenia

AMS=Altered Mental Status | HTN=Hypertension | CPK=Creatine Kinase | SCr=Serum Creatinine

Jordan RM. Myxedema coma: Pathophysiology, therapy, and factors affecting prognosis. *Med Clin North Am.* 1995;79:185-94

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### Myxedema Coma

- Treatment – supportive treatment to correct abnormalities
  - Antibiotics and Steroids
- Thyroid hormone replacement: lack of data to support the use of levothyroxine (T4) versus liothyronine (T3)
  - Levothyroxine 100 – 500 IV mcg bolus
    - Followed by 50 – 100 mcg IV daily until tolerating PO
  - Liothyronine 5 – 20 mcg IV bolus
    - Followed by 2.5 - 10 mcg every 8 hours until improvement
    - Transition to levothyroxine PO
  - Some recommend both be administered concomitantly

Hylander B, Rosenqvist U. Treatment of myxoedema coma—factors associated with fatal outcome. *Acta Endocrinol (Copenh)*. 1985;108:65-71.

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### Factors Known to Precipitate Myxedema Coma

| Other factors                                | Medications           |
|--|-----------------------|
| Burns  | Amiodarone            |
| Carbon Dioxide retention                     | Anesthesia            |
| Gastrointestinal hemorrhage                  | Barbiturates          |
| Hypoglycemia                                 | Beta blockers         |
| Hypothermia                                  | Diuretics             |
| Stroke                                       | Lithium               |
| Surgery                                      | Narcotics             |
| Trauma                                       | Phenothiazines        |
| Infection: pneumonia, influenza, UTI, sepsis | Phenytoin<br>Rifampin |

Jordan RM. Myxedema coma: Pathophysiology, therapy, and factors affecting prognosis. *Med Clin North Am.* 1995;79:185-94  
Lexicomp Online. Lexi-Drugs Online, Hudson, Ohio: Wolters Kluwer Clinical Drug Information, Inc.

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### Special Population - Pregnancy

- Most caused by Hashimoto thyroiditis
- Pregnancy is associated with increase levothyroxine requirements
- TSH levels are decreased in early pregnancy due to hCG
- Patients should start taking an extra dose of levothyroxine 2 days per week for a total of 9 doses per week
- Untreated hypothyroidism can cause spontaneous abortion, preeclampsia, preterm birth, and fetal death



hCG=Human chorionic gonadotropin | PTU=Propylthiouracil | TSH=Thyroid Stimulating Hormone

2017 Guidelines of the American Thyroid Association for the Diagnosis and Management of Thyroid Disease During Pregnancy and Postpartum. Thyroid. 2017;27(3):315-389

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### Audience Participation

On rounds in the ICU, a new admission is diagnosed with myxedema coma and the team has asked what medication and dose to give the patient now. What do you recommend?

- A. Levothyroxine 300 mg IV bolus
- B. Liothyronine 100 mcg IV bolus
- C. Levothyroxine 0.3 mg IV bolus
- D. Liothyronine 20 mg IV bolus

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38

### Audience Participation

On rounds in the ICU, a new admission is diagnosed with myxedema coma and the team has asked what medication and dose to give the patient now. What do you recommend?

- A. Levothyroxine 300 mg IV bolus
- B. Liothyronine 100 mcg IV bolus
- C. Levothyroxine 0.3 mg IV bolus**
- D. Liothyronine 20 mg IV bolus

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**Key Points**

- Hypothyroidism may be treated with thyroid replacement either using levothyroxine, liothyronine, desiccated thyroid or liotrix selected based on patient characteristics
- Important to consider the dosing is different between agents, and that IV to PO for levothyroxine is 0.75:1
- Levothyroxine has many drug interactions and unique administration recommendations
- Be aware of the initial high dose treatment for patients presenting with myxedema coma

D'Piro JT, Talbert RL, Yee GC, Matzke GR, Wells BG, Posey L, eds. Pharmacotherapy: A Pathophysiologic Approach, 10e. McGraw Hill; 2017.

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**EMORY**  
HEALTHCARE

**Hyperthyroidism**

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**Hyperfunctioning Thyroid Gland**

**Primary hyperthyroidism**

- Graves disease
- Toxic adenoma
- Toxic multinodular goiter

**Secondary hyperthyroidism**

- Pituitary adenoma
- Elevated B-HCG (tumors)

**Painless or transient (silent) thyroiditis**

Kovacs L. Hyperthyroidism: Diagnosis and Treatment. Am Fam Physician. 2016;93(5):363-370.

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### Clinical Presentation

|                         |   |
|-------------------------|---|
| <b>Constitutional</b>   | • weight loss, sweating, heat intolerance |
| <b>Neuromuscular</b>    | • psychosis, insomnia, tremor, anxiety    |
| <b>Cardiovascular</b>   | • palpitations, tachycardia               |
| <b>Pulmonary</b>        | • tachypnea, shortness of breath          |
| <b>Reproductive</b>     | • menstrual irregularity                  |
| <b>Gastrointestinal</b> | • nausea, vomiting, hyperdefecation       |
| <b>Ocular</b>           | • exophthalmos, diplopia                  |
| <b>Other</b>            | • increased appetite, goiter, fine hair   |

Kravets I. Hyperthyroidism: Diagnosis and Treatment. *Am Fam Physician*. 2016;93(5):363-370.

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### Treatment

**Antithyroid (ATD) medications**

- Methimazole - preferred except during pregnancy
- Propylthiouracil

**Radioactive iodine ablation**

**Surgical Thyroidectomy**

**Factors to consider when choosing therapy (benefits vs risks)**

- Age, Symptoms, Comorbidities, Patient preference

**Goals of treatment**

- Reduce thyroid hormone synthesis and circulation
- Control peripheral effects and systemic manifestations of thyroid hormone

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### Methimazole

**Drug Class**

- Antithyroid: thioamide

**Mechanism of Action**

- Inhibits the synthesis of thyroid hormones by blocking the oxidation of iodine in the thyroid gland; blocks synthesis of thyroxine and triiodothyronine; does not inactivate circulating T<sub>4</sub> and T<sub>3</sub>

**Dosing**

- Varies upon indication, dose range [5-40] mg/day as a single dose, max 60 mg/day in 2 - 3 divided doses for doses higher than 30 mg/day
- Titrate every 4 to 6 weeks based on free T<sub>4</sub> and total T<sub>3</sub> to achieve euthyroidism

**Side Effects**

- Agranulocytosis (within 90 days of initiation), hepatotoxicity, lupus-like syndrome, pancreatitis, vasculitis, rash

**Clinical Pearls**

- May diminish the anticoagulant effect of VKA and need higher doses of warfarin, should already be monitoring the PT/INR for those patients

VKAs=Vitamin K Antagonists  
Lexicomp Online, Lexi-Drugs Online, Hudson, Ohio: Wolters Kluwer Clinical Drug Information, Inc.

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### Methimazole Dosing

| Dosing Strategies based on Indication             |  |
|---|--|
| <b>Hyperthyroidism associated with Graves</b>     |  |
| Free T <sub>4</sub> levels 1 - 1.5 times ULN      | 5 – 10 mg PO once daily                            |
| Free T <sub>4</sub> levels > 1.5 - 2 times ULN    | 10 – 20 mg PO once daily                           |
| Free T <sub>4</sub> levels > 2 times ULN          | 20 – 40 mg/day in 2-3 divided dose > 30 mg/day     |
| <b>Thyroid Storm</b>                              |  |
| Initial (combination therapy)                     | 20 mg every 4 - 6 hours (PO, NG, Rectal routes)    |
| Clinically Stable                                 | 20 mg daily or BID                                 |
| <b>Thyrotoxicosis (Type 1 Amiodarone Induced)</b> |  |
| Initial monotherapy (Type 1)                      | 30 – 40 mg daily (divided doses for long duration) |
| Unknown etiology (Type 1 vs 2)                    | Glucocorticoid + methimazole                       |

ULN=Upper Limit of Normal  
Lexicomp Online, Lexi-Drugs Online, Hudson, Ohio: Wolters Kluwer Clinical Drug Information, Inc.

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### Propylthiouracil – PTU

**Drug Class**

- Antithyroid: thioamide

**Mechanism of Action**

- Inhibits the synthesis of thyroid hormones by interfering with TPO which inhibits the reaction between MIT and DIT to form T<sub>4</sub> and T<sub>3</sub>. Blocks conversion of T<sub>4</sub> to T<sub>3</sub> in peripheral tissues

**Dosing**

- Varies upon indication, dose range 300 - 900 mg/day in 3 divided doses (8-hour intervals)

**Side Effects**

- Boxed Warnings: Hepatotoxicity (severe liver injury, acute liver failure)
- Bleeding, bone marrow suppression, dermatitis, fever, hypothyroidism, lupus-like syndrome, nephritis, pneumonitis, vasculitis

**Clinical Pearls**

- May diminish the anticoagulant effect of VKA and need higher doses of warfarin
- Preferred agent during the first trimester of pregnancy

MIT=Moniodotyrosine | DIT=Diiodotyrosine | TPO=Thyroid Peroxidase | VKA=VitaminK Antagonists  
Lexicomp Online, Lexi-Drugs Online, Hudson, Ohio: Wolters Kluwer Clinical Drug Information, Inc.

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### Propylthiouracil Dosing

| Dosing Strategies based on Indication   |   |
|---|---|
| <b>Hyperthyroidism associated with Graves</b>   |   |
| Initial   | 50 – 150 mg TID                                 |
| Severe (free T <sub>4</sub> > 2 times ULN)  | Doses up to 800 mg/day                          |
| Pregnancy   | 50 mg 2 – 3 times daily; doses up to 300 mg/day |
| <b>Hyperthyroidism</b>  |   |
| Initial   | 300 mg/day (divided doses), 400 mg/day          |
| Maintenance   | 50 – 150 mg TID                                 |
| <b>Internal contamination with radioactive iodine: potassium iodide not an option</b> |   |
| Patients > 40 years of age  | 100 mg TID x 8 days                             |
| <b>Thyroid Storm</b>  |   |
| In combination (until clinically stable)  | 500 – 1000 mg LD, 200 – 250 mg q4h MD           |

ULN=Upper Limit of Normal | LD=Loading Dose | MD=Maintenance Dose  
Lexicomp Online, Lexi-Drugs Online, Hudson, Ohio: Wolters Kluwer Clinical Drug Information, Inc.

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### Methimazole versus PTU

- Methimazole is preferred over PTU due to hepatotoxicity concerns
- Onset of action quicker for methimazole than PTU
  - Methimazole: 12 to 18 hours
  - PTU: 24 to 36 hours
- Conversion between methimazole to propylthiouracil is a ratio of 1:20 is recommended when switching from one drug to another (100 mg PTU = 5 mg methimazole)

PTU=Propylthiouracil  
The efficiency and safety of methimazole and propylthiouracil in hyperthyroidism: A meta-analysis of randomized controlled trials. *Medicine*. July 30, 2021 - Volume 100 Issue 30 - p e26707 doi: 10.1097/MD.00000000000026707  
Nakamura N, Noh H, Koh N, Fukuta S, Miyasuchi A, Hamada N. Comparison of methimazole and propylthiouracil in patients with hyperthyroidism: a meta-analysis. *Ann Endocrinol Metab*. 2007;93(6):2157-2162. doi:10.1210/er.2006-2135

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### Audience Participation

Let's convert our patient from methimazole 10 mg once daily to a PTU dose in the setting where she will be trying to conceive.

- A. PTU 200 mg/day
- B. PTU 100 mg/day
- C. PTU 200 mg TID
- D. PTU 300 mg BID

PTU=Propylthiouracil

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### Audience Participation

Let's convert our patient from methimazole 10 mg once daily to a PTU dose in the setting where she will be trying to conceive.

- A. PTU 200 mg/day**
- B. PTU 100 mg/day
- C. PTU 200 mg TID
- D. PTU 300 mg BID

PTU=Propylthiouracil

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### Meta Analysis – Methimazole/PTU

| The efficiency and safety of methimazole and propylthiouracil in hyperthyroidism (n=1906)   |  |
|---|--|
| <b>Objective</b>  | 16 RCTs were used in this meta-analysis with 973 patients receiving MMI and 933 receiving PTU<br>Aim was to evaluate the efficiency and safety of methimazole and PTU in the treatment of hyperthyroidism  |
| <b>Method</b>   | Primary outcomes: clinical efficacy and thyroid hormone levels<br>Secondary outcomes: liver function indexes and adverse reactions<br>Results were expressed as weighted mean difference (WMD) or odds ratio (OR)  |
| <b>Patient Characteristics</b>  | Inclusion criteria were hyperthyroidism patients based on clinical symptoms: metabolic syndromes such as heat intolerance, sweating, flushing, tremor, increased appetite, hyperphagia, ophthalmic signs, along with laboratory results  |
| <b>Results</b>  | Levels of T <sub>3</sub> (WMD = -1.321, 95% CI: -2.271 to -0.372, P=0.006)<br>Levels of T <sub>4</sub> (WMD=-37.311, 95% CI: -5.972 to -1.255, P=0.003)<br>Risk of liver function damage (OR=0.208, 95% CI: 0.146-0.269, P < 0.001)<br>Risk of hypothyroidism (OR=2.738, 95% CI: 1.444-5.193, P=0.002) |
| MMI might have a higher risk of hypothyroidism than PTU, the efficacy of MMI may be better than PTU in patients with hyperthyroidism regarding reducing T <sub>3</sub> , T <sub>4</sub> , FT <sub>3</sub> , and FT <sub>4</sub> levels, decreasing the risk of liver function damage and increasing the level of thyroid-stimulating hormone. |  |

PTU=Propylthiouracil | RCT=Randomized Control Trial | MMI=Methimazole | WMD=Weighted mean Difference | OR=Odds Ratio | CI=Confidence Interval

The efficiency and safety of methimazole and propylthiouracil in hyperthyroidism: A meta-analysis of randomized controlled trials. *Medicine*. July 30, 2021 - Volume 100 Issue 30 - p.e26707 doi: 10.1097/MD.00000000000026707

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### Beta-Blockade Treatment

| Nonselective B-adrenergic receptors   |   |  |
|---|---|--|
| Drug  | Dosage  | Comments   |
| <b>Propranolol</b>  | 10 – 40 mg TID – QID  | Preferred agent in nursing/pregnancy<br>Partially block conversion of T4 to T3 |
| <b>Nadolol</b>  | 40 – 160 mg Daily   | Partially block conversion of T4 to T3   |
| <i>Symptom management due to clinical manifestations mediated by beta-adrenergic receptors in hyperthyroidism</i> |   |  |
| <b>Use</b>  | Help with palpitations, anxiety, tremor, heat intolerance   |  |
| <b>Efficacy</b>   | Lower HR, improved fatigability, less SOB, and improved physical functioning after four weeks of therapy from one RCT |  |
| <b>Contraindicated</b>  | Patients with decompensated HF  |  |
| <b>Caution</b>  | Use caution in those with reactive airway disease (asthma, COPD)  |  |
| <b>Side-Effects</b>   | Nausea, vomiting, bradycardia, light-headedness   |  |

BB=Beta Blockers | HF=Heart Failure | HR=Heart Rate | SOB=Shortness of Breath | RCT=Randomized Control Trial | COPD=Chronic Obstructive Pulmonary Disease

Tagami T, Yambe Y, Tanaka T, et al. Short-term effects of β-adrenergic antagonists and methimazole in new-onset thyrotoxicosis caused by Graves' disease. *Intern Med*. 2012;51(17):2285-2290. doi:10.2169/intermedicine.51.7302

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If DD our patient went untreated, thyroid storm can occur!

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### Thyrotoxic Crisis

- Initial presentation: decompensated thyrotoxicosis
  - High fever, tachycardia, tachypnea, dehydration
  - GI symptoms including nausea, vomiting, and most severe jaundice
  - Neurologic symptoms: delirium and coma
- Underlying thyrotoxic condition most commonly Graves disease
- Caused by some precipitating event!
  - Surgery, trauma, MI, PE, DKA, severe infection, RAI treatment, and ATD withdrawal
- Utilize the **Burch-Wartofsky** point scale for diagnosis
- Duration 72 hours but symptoms can persist up to 8 days

MI=Myocardial Infarction | PE=Pulmonary Embolism | DKA=Diabetic Ketoacidosis  
RAI=Radioactive Iodine | ATD=Anti-Thyroid Drug

Nayak B, Burman K. Thyrotoxicosis and thyroid storm. Endocrinol Metab Clin North Am. 2006;35(4):663-686. vii.

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### Thyrotoxic Crisis



- Supportive Treatment
  - Airway, oxygen, IV fluids, cooling blanket
- Inhibit T<sub>4</sub> and T<sub>3</sub> synthesis (thioamides)
  - Propylthiouracil over Methimazole
    - PTU interferes with the production of thyroid hormone, also blocks peripheral conversion of T<sub>4</sub> and T<sub>3</sub>
- Inhibit T<sub>4</sub> and T<sub>3</sub> release (rapidly)
  - Iodide
    - Administer after a thioamide has been given to inhibit iodide utilization by the overactive gland to prevent it from being used as a substrate
- Heart rate control
  - Beta-blockade
- Inhibits peripheral conversion of T<sub>4</sub> into T<sub>3</sub> and improve outcomes
  - Corticosteroids

Nayak B, Burman K. Thyrotoxicosis and thyroid storm. Endocrinol Metab Clin North Am. 2006;35(4):663-686. vii.

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### Thyroid Storm Drugs and Doses

| Drug                                       | Dosing  | Comments  |
|--|---|---|
| <b>Propylthiouracil</b>                    | 500 - 1000 mg load, then 250 mg every 4 hours | Blocks new hormone synthesis<br>Blocks T <sub>4</sub> → T <sub>3</sub> conversion                 |
| <b>Methimazole</b>                         | 60 – 80 mg/day                                | Blocks new hormone synthesis  |
| <b>Propranolol</b>                         | 60 – 80 mg every 4 hours                      | Monitor in CHF patients<br>Blocks T <sub>4</sub> → T <sub>3</sub> conversion (high doses)         |
| <b>Iodine (saturated potassium iodide)</b> | 5 drops (0.25 mL/250 mg) orally every 6 hours | Do not start until 1-hour after antithyroid drugs   |
| <b>Hydrocortisone</b>                      | 300 mg IV load, 100 mg every 8 hours          | May block T <sub>4</sub> → T <sub>3</sub> conversion<br>Prophylaxis against adrenal insufficiency |

CHF=Congestive Heart Failure | T<sub>2</sub>=Triiodothyronine | T<sub>4</sub>=Thyroxine

Lexicomp Online, Lexi-Drugs Online, Hudson, Ohio: Wolters Kluwer Clinical Drug Information, Inc.

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### Medications Beware!

| Medications  | Timing onset following initiation |
|--|-----------------------------------|
| Amiodarone   | Months to years                   |
| Interferon-Alpha   | Months                            |
| Interleukin-2 (IL-2); Aldesleukin  | Months                            |
| Alemtuzumab  | 17 months                         |
| Lithium  | > 1 year                          |
| Iodinated contrast   | Weeks to months                   |
| Tyrosine Kinase Inhibitors (TKI): <i>nilotinib, sorafenib, sunitinib</i>       | 3 – 12 months                     |
| Programmed death receptor-1 (PD-1) inhibitors: <i>Nivolumab, Pembrolizumab</i> | 6 weeks to years                  |

Braunstein, G. D. (2022, November 14). *Hyperthyroidism - endocrine and metabolic disorders*. Merck Manuals Professional Edition  
Lexicomp Online, Lexi-Drugs Online, Hudson, Ohio: Wolters Kluwer Clinical Drug Information, Inc.

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### Special Population - Pregnancy

- Common cause is Graves' disease (0.2%)
- Transient: severe morning sickness leads to high hCG
- Treatment indicated to prevent early labor, pre-eclampsia, and lower risk of thyroid storm

|  |  |  |
|--|--|--|
| 1 <sup>st</sup> TSH [0.05 – 3.70] mIU/mL | 2 <sup>nd</sup> TSH [0.31 – 4.35] mIU/mL | 3 <sup>rd</sup> TSH [0.41 – 5.18] mIU/mL |
|--|--|--|

|                 |                   |                  |
|-----------------|-------------------|------------------|
| First; 0-13 wks | Second; 14-26 wks | Third; 27-40 wks |
|-----------------|-------------------|------------------|



PTU preferred due to fetal toxicity with methimazole  
Beta-Blocker

Can switch to Methimazole  
Surgery: removal of thyroid gland safest in 2<sup>nd</sup> trimester  
Beta-Blocker

Can switch to Methimazole  
Beta-Blocker: only required until controlled with antithyroid therapy

hCG=Human chorionic-gonadotropin | PTU=Propylthiouracil | TSH=Thyroid Stimulating Hormone  
2017 Guidelines of the American Thyroid Association for the Diagnosis and Management of Thyroid Disease During Pregnancy and Postpartum. Thyroid. 2017;27(3):315-389

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### Audience Participation

If our patient DD was 31 and was 10 weeks pregnancy but has just been diagnosed with hyperthyroidism. What medication would you recommend to start treatment?

- PTU
- Methimazole
- Radioactive iodine
- Carbimazole
- Levothyroxine

PTU=Propylthiouracil

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## Audience Participation

If our patient DD was 31 and was 10 weeks pregnancy but has just been diagnosed with hyperthyroidism. What medication would you recommend to start treatment?

- A. PTU
- B. Methimazole
- C. Radioactive iodine
- D. Carbimazole
- E. Levothyroxine

PTU=Propylthiouracil

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## Now were back. . .

**Patient Case - DD**

DD is a 71-year-old female with a past medical history of T2DM, HTN, and multinodular thyroid goiter (dx biopsy 2018) who presents to the ED after a fall in the setting of four weeks of progressive generalized weakness, weight loss, and decreased appetite.

- Home medications (noncompliant)
  - Sitagliptin 100 mg daily
  - Bisoprolol/HCTZ 5/6.25 mg daily
  - Losartan 25 mg daily
  - Gimepiride 2 mg daily



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## Patient Case Summary

Discharge medications: **Propranolol 20 mg daily, Methimazole 10 mg daily**

Per chart review methimazole was increased to 15 mg daily during October

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### Key Points

- Hyperthyroidism may be treated with antithyroid drugs, radioactive iodine, or surgical removal of thyroid gland selected based on patient characteristics
- Methimazole and PTU have similar efficacy in reducing thyroid hormone synthesis, with response seen in 4 to 6 weeks
- Important to consider the dosing is different between agents, and PTU may have more side effects
- Beta blockers are used as adjunctive therapy to control adrenergic symptoms due to the underlying disorder

PTU: Propylthiouracil  
DiPiro JT, Talbert RL, Yee GC, Matzke GR, Wells BG, Posey L, eds. Pharmacotherapy: A Pathophysiologic Approach, 10e. McGraw Hill; 2017.

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### Pharmacist's Role

- Provide patient education on side effects, monitoring, and adherence to thyroid replacement or antithyroid regimen
- Review patient medications for drug interactions
- Assess patient specific factors for appropriate treatment strategies and dosing
- Counsel patients on the importance of adherence and lab frequency with follow up

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### Acknowledgements

- Heidi King Berman, PharmD, BCPS

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**EMORY**  
HEALTHCARE

## Review of Thyroid Disorders



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