GOALS OF THERAPY:
- Normalize TSH and fT4 levels
- Eliminate symptoms
- Avoid over-supplementation

PREVENTING HYPOTHYROIDISM IN PREGNANCY:
- Concern: impaired fetal cognitive development and increased fetal mortality
- Women who are planning pregnancy or currently pregnant should supplement their diet with a daily oral supplement that contains 250 ug of iodine (as KI)
  - > Except pregnant women being treated for hyperthyroidism or who are taking T4
- TSH screening for hypothyroidism is indicated in women who are planning pregnancy or are in early pregnancy *if they have a goiter or strong family hx of thyroid disease*
- Euthyroid but TPO/antibody positive pregnant women should have TSH measured at time of pregnancy confirmation, and every 4 wks through mid-pregnancy
  - > Unknown if T4 supplementaiton reduces preterm delivery in these people

TREATING PRIMARY HYPOTHYROIDISM IN PREGNANCY:
- **Treat with T4 if TSH 4.0 mU/L**
  - If hypothyroidism was diagnosed before pregnancy: increase L-thyroxine intake by 20-30% immediately
  - If hypothyroidism is diagnosed during pregnancy: T4 dose should be rapidly titrated to normalize TSH levels
- TSH q4 wks until 20 wks, and at least once at 30 wks
  - Estrogen-induced increase in TBG results in increased binding of T4, lowering free T4 levels
  - T4 requirements increase during pregnancy until 16-20 wks, then plateau
- **Target TSH: 0.4 – 2.5 mU/L** throughout pregnancy
- Return to preconception T4 dose following delivery and measure TSH at 6 weeks

TREATING PRIMARY HYPOTHYROIDISM IN LACTATION:
- Only very low quantities transferred into human milk
- Not sufficient to affect plasma thyroid hormone levels in neonates
- Treatment considered compatible with breastfeeding

CAM IN HYPOTHYROIDISM:
- Dessicated thyroid (porcine, bovine)
  - Inexpensive
  - Variable amounts of T3 & T4 = variable biological activity
  - Not recommended
- Iodine sources
  - Kelp supplements 150-250 mcg/capsule
  - Iodine RDI is 150 mcg/d
- 3 dothyroacetic acid (TRIAC; tiratricol)
- L-tyrosine
- Selenium
  - ↑ subjective well-being ?
  - ↓ anti-TPO Ab?
- Thyroid enhancing preparations – NO EVIDENCE
  - Natural herbs/fruits/veggies

SYNTHETIC L-THYROXINE (T4):
- Monotherapy is drug of choice when initiating therapy
  1. Initial dosing:
     - Young healthy adults: **1.6 mcg/kg** (full replacement dosage)
     - Elderly: 50 mcg/d
     - CAD: 12.5 – 25 mcg/d (monitor for angina)
  2. Re-measure TSH 4-8 weeks after initiation or dose change
     - Draw blood before daily dose if measuring fT4 (due to 20% rise 3.5 – 9 h after dose)
     - No real role for measuring T3/fT3
  3. Adjust doses in **12.5 – 25 mcg/d increments**, sometimes smaller (rarely larger)
  4. Once on appropriate dose, measure TSH annually, and when conditions changes

- ADME / counselling tips:
  - Long $t_{1/2}$ (7 days) = once daily administration
  - Takes 5-6 weeks for steady state to be reached
  - Approx. 60-80% of administered dose is absorbed in small intestine
    - Absorption reduced by food, some drugs
    - Better absorption when taken at HS and on empty stomach
  - If dose missed, take it when remembered – even if its hours or days later

- No clinical advantage (QOL, symptoms, cognition) to aiming for lower end of normal TSH range (<2) vs. upper end (>2)

- Relatively narrow therapeutic index
- Over-treatment associated with:
  - Subnormal TSH levels
  - S/S of hyperthyroidism
  - Increased risk of cardiac arrhythmias (AFib)
  - Osteoporosis: reduced bone density; increased risk of osteoporotic fracture if TSH < 0.1

LIOTHYRONINE: SYNTHETIC T3
- Rapid onset, short duration = fluctuating levels, often requires twice daily administration
- More potent than thyroxine = more likely to cause adverse cardiac effects
- Results in high T3 and low T4 levels
- Not recommended for routine treatment
  - T4/T3 combos not superior to T4 alone in body weight, lipids, sx, cognition, QOL

DRUG-RELATED CAUSES OF HYPOTHYROIDISM

Absorption interference	
Reducing stomach acidity	Antacids, PPI, H2 blockers
Binding & preventing absorption	Calcium, iron, Al supplements; cholestyramine; sucralfate; coffee?
Induce hepatic microsomal enzymes & increase T4 breakdown	Rifampin; phenytoin
Inhibited T4 → T3 conversion	Propranolol, atenolol, alprenolol, PTU, dexamethasone, prednisone, iopanoic acid, amiodarone
Inhibited T3/T4 production	Iodine, amiodarone, lithium. PTU, MMI, I131, aminoglutethimide
Inhibited TSH release	Dopamine, dobutamine, octreotide (>100 mcg/d), prednisone (>20 mg/d), metformin? Carbamazepine?
Increased TBG levels	Estrogen, tamoxifen, raloxifene, methadone, fluorouracil, mitotane
Displacement from TBG	Carbamazepine, phenytoin
Thyroiditis	Interferon, interleukin-2, amiodarone, sunitinib

SUBCLINICAL HYPOTHYROIDISM: TSH > 4.5 with normal Ft4
- Concerns: development of overt hypothyroidism; hyperlipidemia; CAD in pts < 60 y/o; cognition
- Management: no evidence that treatment alters outcome
  - Regular thyroid monitoring to detect overt hypothyroidism
- Consider treatment if:
  - Pregnant – may reduce preterm delivery
  - Elderly – possibly improved BMI, BP
- If treating, use low-dose T4 (25 – 75 mcg/d)

GOALS OF THERAPY:
- Normalize TSH, fT4 levels
- Eliminate symptoms

I^{131}/RAI RADIOABLATION:

Advantages	Disadvantages
• Curative (90% at 6-18 wks) • Cost-effective • PO as solution or capsule	• Permanent hypothyroidism • May worsen opthalmopathy • May worsen hyperthyroidism temporarily • Must defer pregnancy 6-12 mos

MECHANISM OF ACTION:
- Concentrated in thyroid, incorporated into thyroid hormone and stored in colloid
- Emits ionizing beta radiation in thyroid gland, destroying functional and regenerative capacities (extent depends on dose)
- Half-life = 8 days; 99% radiation expended within 56 days

USES:
- In older pts, those not surgical candidates or with cardiac disease
- In recurrent/persistent hyperthyroidism following anti-thyroid drugs

STRATEGY:
- **GOAL:** high dose (10-15 mCi) to render pt hypothyroid
- Stop MMI 2-3 days before RAI to prevent failure
- Start B-blocker before RAI to prevent acute S/S
- If severe opthalmopathy: give prednisone 20-40 mg/d x 2-3 months starting 5-7 days after RAI
- Consider re-starting MMI 3-7 days after RAI txt if thyrotoxicosis risk
  - HF, AF, stroke, pulmonary HTN, CRF, COPD, poor controlled DM
- Avoid sharing cups/utensils, sexual contact, close contact with children and pregnant women x 1 wk
- Treat radiation thyroiditis (1%) with NSAIDs
- Delay pregnancy for 6-12 months after therapy

MONITORING:
- Measure TSH, fT4, T3 1-2 months after RAI, then q4-6 wks x 6 months (or until hypothyroid and stable on T4 replacement)
- Re-treat with RAI if still hyperthyroid at 6 months

THYROIDECTOMY:

Advantages	Disadvantages
• Curative • Universally effective • Rapid • Especially useful if large goiter	• Invasive, scar • General anesthetic • Permanent hypothyroidism • Complications (hypoparathyroidism → hypocalcemia, laryngeal nerve damage)

B-BLOCKERS:
- Effective for symptoms, regardless of cause of hyperthyroidism
  - Palpitations, tachycardia, tremulousness, anxiety, heat intolerance
- High dose propranolol reduce peripheral deiodination of T4 (to T3)
- Used in: symptomatic hyperthyroid pts, esp. elderly with HR > 90 or CVD
  - Also in preparation for surgery and in thyroid storm
- DOSES:
  - Propanolol 10-40 mg TID – QID
  - Atenolol 25 – 100 mg OD – BID
  - Metoprolol 25 – 50 mg BID – TID
  - Nadolol 40 – 160 mg OD
  - Esmolol IV pump 50-100 ug/kg/min (ICU)

IODINE:
- Large doses → rapid inhibition of TH release; decrease TH synthesis
  - Used in preparation for surgery and thyroid storm
- KI administered shortly before or after I^{131} exposure blocks I^{131} uptake by thyroid due to saturation of the gland by stable I^-
  - KI 100 mg (50 mg children 3-12 yo) provides 1 day of protection

THERAPEUTIC OPTIONS:
- I^{131}/RAI ablation – 70% of N.A. endocrinologists prefer
- Chronic thionamides
- Thyroidectomy (limited to drug failure, massive goiter, coexisting malignancy)

SIMILAR 6-week biochemical outcomes, similar pt satisfaction & sick leave at 2 yrs

CHRONIC THIONAMIDES:

Advantages	Disadvantages
• Non-invasive • No permanent hypothyroidism • Possible remission	• Not curative • Inconvenience/compliance • Drug toxicity

USE OF ANTI-THYROID DRUGS:
1. As primary treatment of Graves' disease
   - Goal: achieve clinical & biochemical euthryoidism in 3-8 weeks
   - If relapse after remission, consider I^{131} or surgery
2. To produce euthyroidism prior to surgery or radioiodine
   - Reduces vascularity of gland and likelihood of releasing large amounts of stored hormone during the procedure
3. Treatment of choice for hyperthyroidism in pregnancy
   - Goal: maintain maternal fT4 in upper normal range with lowest possible dose to reduce risk of fetal hypothyroidism
   - Also considered safe for nursing mothers
4. Thyroid storm

MECHANISM OF ANTITHYROID DRUGS:
- Concentrated in thyroid, uptake is stimulated by TSH and ↓ by iodide
- Reduce thyroid hormone synthesis by competitively inhibiting TPO
  - Act as alternate substrate and become iodinated and inactivated
- Does not affect hormone release from gland
- Immunosuppressive effects (decrease TRAb)

MMI vs. PTU:

	MMI	PTU

Use	Almost always preferred	• Just before pregnancy & during 1st trimester
		  ○ Less placental transfer
		  ○ No congenital aplasia cutis
		• Thyroid storm (thyrotoxicosis)
		  ○ Inhibits T4 → T3 conversion (unlike MMI)
		• Intolerance/allergy to MMI

Dosing	10-15 mg PO OD (20-30 mg if large goiter)	100 mg PO TID (150 mg if large goiter)
Effect	More rapid improvement in T4, T3 levels	

Adverse effects	• Minor: mild skin rash, GI upset, arthralgias
	• Major: agranulocytosis (within first 3 m)
	  ○ Can develop rapidly but reversible if D/C
	  ○ Cross-reactivity (but less common in MMI)	

		• Hepatotoxicity • Vasculitis (ANCA +ve)
Monitor	• CBC & LFTs at baseline before starting • q4 weekly fT4 and T3 until TSH normalizes (may take several months) • Report first sign of fever, pharyngitis, mouth ulcer (agranulocytosis) or abd. pain,dark urine, changes in stool (hepatotoxicity)	
Remission	• If low/zero TRAb and TSH at 12-18 months, taper down to assess for remission (= normal TSH, fT4, total T3 for 1 year after D/C thionamide) • Relapse worse for men, smokers, large goiters, ↑ TRAb	

GRAVE'S OPTHALMOPATHY / ORBITOPATHY:
- 1 point for each of eyelid erythema/edema, conjunctiva injection, caruncular swelling, chemosis, retrobulbar pain, pain with eye movement
- Score > 2 = active disease

COMPARISON OF CHARACTERISTICS OF ANTITHYROID DRUGS AND RADIOACTIVE IODINE:

	Antithyroid drugs	Radioactive iodine
Time to sx improvement	2-4 weeks in 90% of pts	4-8 weeks in 70% of pts
Recurrence	60-70%	5-20%
Adverse effects	Minor in 5%, Major < 1%	< 1%
Pregnancy	PTU in 1st trimester, then MMI	Contraindicated
Severe ophthalmopathy	No adverse effects	May worsen after txxt
Very large goiter	Recurrence risk	Requires larger dose
Childhood	Long-term treatment often necessary	Not used in < 10 years old

SUMMARY: MECHANISMS OF ACTION OF SOME ANTI-THYROID DRUGS:

Mechanism	PTU	MMI	Lithium	Iodide	BB
Block thyroid I^- uptake			++		
Block hormone synthesis	+++	+++	++	+	
Block hormone release			++	+++	
Block T4 to T3 conversion	++				+
Block adrenergic sx					+++

SUBCLINICAL HYPERTHYROIDISM: TSH < 0.1 + normal fT4

- Increased total and CHD mortality, sudden cardiac death, AFib, fractures
- Possibly more risk in men
- Progresses to hyperthyroidism
- Management: in absence of underlying hyperthyroid diagnosis (e.g. Graves), no evidence that treatment alters any of these outcomes
  - If not treating, regular thyroid monitoring all pts to detect overt hyperthyroidism
- Treatment is same as overt hyperthyroidism, consider in pts:
  - > 65 years old, CVD risk factors or CVD, osteoporosis, postmenopausal women not on estrogen or bisphosphonate, anyone with symptoms

DRUGS THAT CAUSE THYROID DYSFUNCTION:

AMIODARONE:

- Iodine-containing anti-arrhythmic drug that is also structurally similar to thyroid hormones
  - 200 mg dose results in release of approx. 6 mg of free iodine (40x higher than RDA)

AMIODARONE EFFECTS ON THYROID:

- Acute, transient suppression of thyroid function
- Amiodarone-induced hypothyroidism (AIH) in pts susceptible to inhibitory effects of ↑iodine
- Amiodarone-induced thyrotoxicosis (AIT)
  - Type 1 AIT: associated with underlying thyroid abnormality (preclinical Graves disease or nodular goiter)
  - Type 2 AIT: destructive thyroiditis, occurs in pts w/ no intrinsic thyroid abnormalities

EFFECTS OF AMIODARONE ON THYROID FUNCTION <u>DUE TO INTRINSIC EFFECTS OF DRUG:</u>

- Inhibits deiodinases D1 and D2, uptake of T4 and binding of T3 to its receptor
  - Results in decreased T3 in peripheral tissues and pituitary
- Associated with transient elevation of TSH (for 2-3 months), following which TSH normalizes although total and fT4 remain slightly elevated

EFFECTS OF AMIODARONE ON THYROID FUNCTION <u>DUE TO EXCESS IODINE:</u>

- Disrupts thyroid hormone synthesis and autoregulation
- Can result in either AIH (more likely if iodine intake is adequate) or AIT (if low iodine intake)
  - AIH more common in N. America (10-20% of treated pts)
    - Due to inhibition of iodine uptake and oxidation in thyroid because of excess circulating iodine
    - Normally transient, but in susceptible pts can be long-term and result in overt hypothyroidism

LITHIUM:

- Used in treatment of bipolar disorder
- Concentrated in thyroid gland and inhibits iodine intake, iodotyrosine coupling and release of thyroid hormone
- Compensatory mechanisms prevent development of hypothyroidism in majority of pts, however 5-10% will develop clinical hypothyroidism
  - Higher risk in women, especially those starting lithium at ages 40-59