THYROID DISORDERS

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CLINICAL PEARLS

1. Wait **6-8 wks** after LT4 dose change before rechecking **TSH**.
2. Correlate what has happened in **last 8 weeks** to the pt when interpreting TFT's (TSH, FT4, FT3).
3. If **nodule >1cm & history unknown** then do a fine needle aspiration biopsy (FNAB).
4. If LT4 tx response poor, consider **compliance, malabsorption celiac dx, drug interactions (Ca^{++}, Fe^{++}, antacids, etc…) & other diagnosis (eg. adrenal).**
5. Thyrotoxicosis: 1st do FT4/FT3, I-131 uptake & scan, β-blocker, then **MMI/PTU** after discussing all options with the patient.
6. Hyperthyroid diagnosis often missed.

Classification of Thyroid Disorders [1, 2, 3, 4, 5, 6, 7, 8, 9] (American Thyroid Association-ATA, American Association of Clinical Endocrinologists-AACE, British Thyroid Association-BTS, Endocrine Society - ES)

	Normal (values vary; check standard for lab)	HYPOthyroid	Subclinical HYPOthyroidism	HYPERthyroid	Subclinical HYPERthyroidism
TSH ultra- sensitive	0.45–4.5 mIU/L* Euthyroid: TSH <4 –don't treat	↑↑ (>10)	↑ (4-10) (guidelines vary)	↓↓ (<0.1)	↓ (<0.3)
FT4 free T4	9 – 19 pmol/L	↓↓	Normal	↑↑	Normal
FT3 free T3	2.6 – 5.7 pmol/L	↓ not useful for hypo or tx	Normal	↑ pure T3 toxicosis common	Normal

COMMENTS: Total T3 & Total T4 not useful for surveillance or used with current treatment goals or guidelines.

- **Seriously ill Pt**→ TFTs not assessed unless strong suspicion of thyroid dx. LT4 tx of little benefit & may be harmful.
- **TSH**: Best screening test for hyper/hypothyroidism (draw blood in **am**). **If abnormal measure FT4 & FT3. Clinical assessment & tx based on SYMPTOMS**. Will not identify pts with pituitary or hypothalamic disease.
- **FT4:** More accurate than TSH in unstable thyroid state e.g. recent hyperthyroidism tx, on excess T4 replacement.↑/↓ in a clinically hyper/hypothyroid pt, with non-suppressed/elevated TSH = 2° causes.
- **FT3:** May be useful early in tx to assess level of **active** hormone.

SCREENING: Reasonable in ↑risk pts ♀**>45,** pregnancy/postpartum, **strong family hx, goiter, S&S, autoimmune dx (e.g. T1DM), vitiligo, neck radiation, pernicious anemia, ↑lipids, hypoadrenalism, hx of thyroid surgery/dx. psychiatric dx, amiodarone/lithium, Down's/Sjogren Syndrome.** [1, 4, 7, 10] Routine adult screening controversial →? clinical benefit, ? cost effectiveness. [6, 7, 10] * Possible Δ to upper TSH limit→ ? ↓ to 2.5 $_{mIU/L}$ →No evidence of AE for TSH 2.5-5 $_{mIU/L}$; level limitations **assay problem, circulating abnormal TSH, etc** ; may ↑pts diagnosed as subclinical.

HYPOthyroidism Prevalence: ~2% of ♀, 0.1% of ♂; ↑'s with age

SYMPTOMS: ↓HR, fatigue, ↑wt, **cold** intolerance, dry skin/hair, constipation, hair loss, menorrhagia, emotional lability, poor concentration & ↑cholesterol

OTHER TESTS: Ultrasound volume, echo texture, nodules; **Not Routine: Anti-TPO** identify autoimmune cause, check if recurrent miscarriages; **Bone Density** if clinically indicated

TYPES & TREATMENT: **1° Hashimoto's Thyroiditis** most common, iatrogenic, congenital, ↓I rare in developed countries

2° ~1% of cases **pituitary** >sx of pituitary insufficiency: abnormal menses, ↓libido, galactorrhea, acromegaloid; **hypothalamus** rare eg. tumor, inflammatory conditions, infiltrative dx, infection, pituitary surgery or radiation, & head trauma → do MRI / CT scan.

1° Hypothyroidism: permanent condition in most pts. Tx: LT4

Myxedema Coma: rare decompensated hypothyroidism: ↓mental status, hypothermia, ↓BP/HR, hypoventilation, esp. elderly. **Tx**:hydrocortisone 100 mg IV q8h until adrenal suppression ruled out; LT4 100-400μg IV Day 1, 50-100μg IV/d until stable→LT4 po

Congenital: asymptomatic at birth maternal hormone crosses placenta; S&S appear after ≥6-12wk: poor feeding, growth failure, lethargy, slow movement, hoarse cry. **Tx**: LT4; Goal= FT4 ≥ upper half of the normal range adjusted for age

MONITORING: LT4 is life long therapy

- **Goal** = TSH & FT4 in normal range ? Goal TSH ≤2.5 mIU/L: TSH >2.5 often have S&S & tx sx's
- Re-evaluate TSH/FT4/ $_{FT3\ too\ variable}$ q6-8wks until stable. TSH can remain abnormal for months→FT4 more reliable indicator initially.
- Clinical improvement in 2 weeks. Complete recovery in several months.
- Once euthyroid: maintenance LT4 dose does not fluctuate greatly → monitor **TSH** q6-**12** months.
- Re-evaluate TSH q6-8 weeks after any **Δ in LT4 brand/dose** or **Δ in wt ≥10lb.**

SUBCLINICAL: [6, 7, 11, 12, 13] elevated TSH & **FT4/T3** within **range** 4-10% of the population.

- Clinical Significance: ? ↑ atherosclerosis, CHD, MI, depression, ↓BMD, metabolic sx. Cochrane review: tx does not improve survival or ↓ CV morbidity. [16]
- TSH >10 $_{mIU/L}$ → recheck TSH in 6-8wks, if still >10 mIU/L→ **Tx**:**LT4** 25-75μg daily
- TSH 4.5-10 $_{mIU/L}$→**consider tx** esp if hypothyroid S&S, DM, ↑lipid, HTN, pregnant/planning, depression,↑↑ goiter, ↑antibody ⊕, HF
- If no tx, monitor q6-12 months for Δ in clinical status & TSH.

PREGNANCY: Hashimoto's autoimmune thyroiditis most common

- Clinical Significance Complications: **Maternal** miscarriage, C-section, gestational HTN/DM, pre-eclampsia→↑↑ hypothyroid risk later, etc. **Fetal** cognitive impairment, lower IQ score, stillbirth, low birth wt, delays in mental/motor development, etc.
- **Tx**: LT4 dose Δ's(↑ dose **25**-50%) → check FT4/**TSH** when pregnant & q**4**wk.
- **Subclinical Hypothyroidism:** limited evidence, monitor for progression.
- Dose ↑ often greater if thyroidectomy/radioablation than with Hashimoto's.

SPECIAL POPULATIONS: Athletes: LT4 not on prohibited substance list. **Elderly** may have atypical sxs. **Elderly >85** + TSH 4.5-10, esp. with CVD: tx only if cognitive sx's etc but go slow with LT4.

DRUG-INDUCED: also see below: ↓T4 absorption: See LT4 DIs (next page)

- **↓TSH secretion:** amiodarone. bexarotene, dopamine, glucocorticoids, hormones endogenous. metformin. somatostatin
- **↓ Hormone synthesis/release:** aminoglutethamide, **amiodarone**, expectorant iodinated glycerol , iodide including x-ray contrast, **lithium**, thalidomide, thionamides & topical antiseptics povidone iodide
- **↓T4→T3 conversion**: amiodarone, β-Blockers, glucocorticoids, x-ray contrast iodinated.
- **↑T4/T3 metabolism:** carbamazepine, phenobarbital, phenytoin & rifampin no effect on normal thyroid function, but ↑LT4 doses may be needed
- **Autoimmune dx induction:** amiodarone, **interferon-α**. interferon- β, interleukin-2 & lithium
- **Unknown mechanism:** sertraline, sorafenib & sunitinib.

HYPERthyroidism especially ♀ 0.6%

SYMPTOMS: ↑HR, tremor, ophthalmopathy, **heat** intolerance, ↓weight ↑rarely, ↑BMR, menstrual Δ's, ↑Ca^{++}, diarrhea, weakness, apathy elderly

OTHER TESTS: Ultrasound volume, echo texture, nodules ; **RAIU & scan** differential once hyperthyroidism established (e.g. thyroiditis has ↓ RAIU, Graves' has diffuse RAIU)
Not Routine: TRAbs ? clinical utility, expensive, long turn around time from lab), helpful in pregnancy to determine fetal risk; **ECG** if cardiac disease, irregular rhythm.

TYPES & TREATMENT: **Graves' Disease** most common esp. in young: both ↑T3 & T4; autoimmune dx due to TRAbs→stimulate thyroid growth, hormone synthesis & release may have proptosis, pretibial myxedema. **Tx**: Thionamide **MMI** or PTU; 1st line Europe, esp ♀ young fertile, RAI destroys gland; 1st line USA; **CI** if active eye dx: steroids may help, surgery scar, symptom control β-Blocker.

- **Solitary Toxic Nodules & Toxic Multi Nodular Goiter** Multi Nodular Goiter: esp older pts, RAIU is ↑ : ↓ TSH, ↑ T3, but a normal T4; autonomous thyroid nodules secrete excess thyroid hormone. **Tx**: Thionamides to attain euthyroid before tx with RAI or surgery; esp. for elderly/CVD/severe sx/ T3,T4 2-3x ULN; or RAI 1st line US; may need ↑dose, often weeks wait time, AE: edema; Surgery; ?ethanol inj . If pretreat with thionamides the required I131 dose will be larger, & cure rate after first tx will be lower.
- **Thyroiditis** painless/subacute. ↑ESR/postpartum: Inflammatory damage to the gland→↑release of T4 & T3; ↓RAIU; initially hyperthyroid likely followed by transient hypothyroid. **Tx**: Self-limiting; β-Blockers; NSAIDs pain control; Glucocorticoids reserved for severe cases; Thionamides not indicated does not ↓ preformed hormone release.
- **Thyroid Storm**: life threatening decompensated thyrotoxicosis fever, tachycardia, dehydration, delirium, coma, nausea, vomiting, diarrhea; causative factors: RAI, trauma, surgery. **Tx**: β-Blocker propranolol 40-80mg po q6h (not long acting form); PTU preferred; Iodide ↑dose, SSKI 5 drop po q6h (Potassium iodide)/Lugol's after PTU; Hydrocortisone ≥100mg IV q8h; Supportive tx.
- **Thyroid Cancer (ca):** papillary, follicular cancers differentiated; anaplastic undifferentiated → arise from differentiated. **Tx**: Surgery→ ?RAI adjuvant ablation ↓dose + withdrawal / thyrotropin alfa → LT4/TSH suppression↓TSH induced tumor growth; If high/immediate ca risk (eg.stage 3-4)→TSH≤ 0.1mIU/L; If ca stage 1-2 →TSH=0.1-0.5 mIU/L [14,15]

MONITORING: Goal=maintain TSH & FT4 in normal range. Re-check TSH/FT4/FT3 q4-6 wks until stable **frequency will depend on severity of illness**. TSH can remain suppressed for months→FT4 more reliable indicator initially. Clinical improvement in 3-4 weeks. In 4-12 weeks most pts are euthyroid or improved considerably **must** ↓ dose of MMI/PTU. Stable dose identified →monitor **TSH** q2-6month depends on illness severity. MMI often 1st, if AE consider PTU.

- **>18 months of tx not associated with improved relapse rates in Graves' disease; often treat until euthyroid for ~1 year.** Relapse ~50% in Graves' occurs within 1st 3 months alternate tx with RAI if hyperthyroidism persists >6months. preferred to 2nd MMI/PTU course ↑ monitoring if d/c MMI/PTU after remission.
- **Nodules:** Do TSH & ultrasound. If TSH low then do I-131 or technetium scan. If nodule is <1cm or unchanged & no family risk→likely not cancer. **FNAB** if: nodule growing; >1cm & history unknown; if ultrasound suggests cancer; family/pt history of thyroid cancer; if neck radiation, or vocal/swallowing problems.

SUBCLINICAL: [6, 7, 16] TSH below lower reference limit & FT4/FT3 within range 2% of the popn. **Lab error common**→ repeat; consider tx only if TSH is persistently low

- **Graves Disease**: more likely to resolve. **Solitary autonomous nodules & multinodular goiter**: more likely to persist or progress.
- Clinical Significance: **osteoporosis** esp. in postmenopausal ♀, cardiac abnormalities esp. **AF/HF in elderly**, mortality ↑41%. Clinical implications may suggest to tx very mild thyroid hyperfunction, even in asymptomatic older pts.
- **Tx**: **↑ risk for complications** eg. elderly, postmenopausal (1) **TSH <0.1 mIU/L**→ tx for hyperthyroidism,
  (2) **TSH 0.1-0.3 mIU/L** → consider tx esp. if thyroid scan shows high uptake or ↓BMD, otherwise observe if medical conditions repeat TSH in 2 wks, or 3 mos otherwise
  ↓ risk for complications e.g younger, healthier (1) **TSH <0.1 mIU/L** → tx for hyperthyroidism esp. if thyroid scan shows high uptake or ↓BMD,
  (2) **TSH 0.1-0.3 mIU/L** → follow up TSH in 3 months

PREGNANCY: Gestational assoc. with hyperemesis gravidarum - if low TSH, check T3 & if ↑, may need tx.
True Grave's thyrotoxicosis- tx 2/1000 pregnancies; Worse during 1st trimester→improve later→worse after delivery. Assess newborn for hypothyroidism if MMI/PTU given. If initial maternal thyroid stimulating **antibodies levels are high**, consult pediatrician early. If need **surgery** → optimal timing is during 2nd trimester.

- Clinical Significance: Complications: **Maternal** miscarriage, preterm labour, HTN, HF, etc. & **Fetal** stillbirth. low birth weight, goiter, etc; **NO RAIU or Scans**
- **Tx**: Mild hyperthyroidism →monitor without tx as long as mother/fetus are not symptomatic; expect altered lab values TSH=low normal; FT4=high normal
  1st Trimester: PTU preferred over MMI congenital malformations. **2nd & 3rd Trimester**: MMI preferred over PTU risk of maternal hepatotoxicity 0.1-0.2%
  FT4/FT3/TSH q 4-6 wk. Maintain FT4 at or slightly above the upper limit of normal by 2nd/3rd trimester most can ↓dose, &~25% can d/c tx.
- **Subclinical Hyperthyroidism:** adverse pregnancy outcomes not reported →tx not currently recommended.

SPECIAL POPULATIONS: Smoking →? worsen ophthalmopathy, ↓remission & response to MMI/PTU, larger goiter at presentation, ↓TSH/↑FT3 during pregnancy.

ADDITIONAL TREATMENT OPTIONS: **β-Blocker**: ↓sx palpitation, anxiety, tremor, heat intolerance; no effect on thyrotoxicosis; Use short acting non-selective β-blocker easy to titrate & withdraw: **propranolol** 20 mg BID, ↓ to d/c, ?metoprolol, ?atenolol.

- **RAI**: defer pregnancy ≥ 6month; Cardiac/Elderly may need thionamide before RAI to ↓stored hormone→ ?↑RAI failure→**d/c MMI/PTU >1wk if feasible** or if iodine 2month before; **CI**: pregnancy/lactation/eye dx active Graves/↑↑goitre. **AE**: hypothyroid: most in 1st yr→3%/yr, thyroiditis esp. if volume ~45mL,?↑ca risk. Follow-up q4-6wk until euthyroid; 6-18wk to work; TSH slow to recover→FT4 more accurate early on.
- **Surgery**: Option for Graves'; Consider if severe ophthalmopathy, large thyroid, drug failure or toxic nodules. **Caution:** thyroid consistency Δ with **RAI** mush **& amiodarone** bubble gum!
- **Iodides**: (SSKI 38mg/drop: 1-2 drop bid pre-op, Lugol's 6.3 mg/drop); Wolff-Chaikoff effect & ↓size/vascularity of gland; rapid effect ↓sx in 2-7 day; short-term effect 1-2 wks usually. **Tx role** very limited: thyroid storm; rapid hormone release inhibition. **AE**: hypersensitivity, salivary gland swelling; iodism metallic taste, burning mouth, GI upset/diarrhea; gynecomastia; **Caution=OTC meds** containing iodine supplements, kelp, herbals for ↓wt can induce hyper/hypothyroidism.

DRUG-INDUCED: also see below: ↑TSH secretion: antipsychotics. metoclopramide. theophylline: **↑thyroid hormone synthesis/release**: amiodarone, iodine povidone-iodine, lithium; **Immune reconstitution**: alemtuzumab, after highly active HIV tx.

Drug-Induced cont.: Amiodarone: causes hypo 5-25% & hyper<5%. **↑ risk if** thyroid dx or family hx, goiter, thyroid antibodies ⊕ → **monitor** TFTs q1mon x3, q3 mos x4-8, then q6-12 mos. **Hypo** Tx=LT4 & continue amiodarone. **Hyper** difficult to distinguish Type 1 or 2; & amiodarone blocks ↑HR & tremor; pt can deteriorate rapidly & if toxic thyroidectomy may be best. **RAIU** & scan rarely helpful; gland saturated with iodine via amiodarone ≥40x daily amount; **Tx**=d/c amiodarone if possible, propranolol ↑dose if able, Prednisone 40-80mg od esp. Type 2, MMI esp. Type 1. **Dronedarone** 400mg po bid with food; ↓effective than amiodarone; ↓ thyroid AE; but ↑ HF. **Lithium**: can cause hypo-≤20%/hyper?non-clinical, goiter in ≤5%. ↑risk elderly, ♀, prior dx. **Monitor** TSH @3 mos, then q6-12 mos. **Hypo** tx=↓lithium dose ideal or LT4. **Hyper** rare tx= d/c lithium.

Generic/TRADE (Strength & forms)	Therapeutic Use, Special Population Considerations & Pharmacokinetics	Adverse Events AE, Contraindications CI, Drug Interactions DI, Monitoring M	Dosing	$/mo
THYROID SUPPLEMENTS FOR HYPOTHYROIDISM - synthetic forms of T4 (LT4) and T3 (LT3)				
Levothyroxine (LT4) ELTROXIN 50,100,150,200,300µg tablet^{ς} SYNTHROID 25,50,75,88,100,112,125,137$^{x▼}$ 150,175,200,300 µg tablet^{ς} **No evidence either brand superior. Considered interchangeable, but less TFT variation if same brand used.** Can give **SL if malabsorption** a problem. {Liquid Drops available in Europe} **Allergies: white pills** do not contain dye. LT4 500µg/10ml vial • IV/IM when rapid repletion is required or po admin precluded • initial 50-80% of established **po** dose	• 1st line for treatment of hypothyroidism • Little or no effect on multinodular **goiter** size. P L **Pregnancy**: ↑LT4 dose by 25-50% during pregnancy. ↑ 2 extra doses/wk once pregnancy confirmed. ↑ LT4 dose to trimester specific TSH targets. Check TSH q4wks for 1st ½ of pregnancy: Pre-conception: TSH < 2.5 mIU/L, 1st trimester: TSH < 2.5 mIU/L, 2nd trimester: TSH ≤ 3 mIU/L, 3rd trimester: TSH ≤ 3.5 mIU/L **>50yrs without CVD or <50yrs with CVD**: 25-50 µg/day, ↑by 25 µg q6-8 wks prn. More cautious titration to minimize CV risk **Elderly with CVD**: 12.5-25 µg/day, ↑q4-8wk. If ↑CVD S&S: ↓dose. **Severe dx**: 12.5-25 µg/day & ↑25 µg/d q2-4wk until TSH normal **Congenital Hypothyroidism**: Initial 8-15µg/kg/day **~25-50 µg/day** AAP recommends 50 µg/day initially for term & full-size infants **Hx Anxiety or Depression**: start slowly with LT4 replacement **Subclinical**: TSH >10 mIU/L x2, LT4 25-75 µg/day **Pharmacokinetics: Peak** effect: **2-4**hr; **$t_{1/2}$**: 6-7day; **Absorption**: 40-80% ↓ by age / food / med **Protein** bound: 99%	**AE**: ~20% due to **over** treatment, titrate carefully to minimize - palpitations, ↑ HR, tremors, anxiety, diarrhea, etc; may aggravate existing CVD (arrhythmias, AF, angina, MI); ?↓BMD Turner'11 **CI**: acute MI, untreated adrenal insufficiency; obesity/wt loss tx: may produce serious/life threatening AE, esp if given with certain weight reduction aids. Does not ↑ thyroid cancer. **DI**: Check TSH 6-8wks after interacting medication started, dose ↓↑ or discontinued. Space administration from LT4: • **Space ≤**1hr: coffee/tea 1hr, meals 30min • **Space >2-4hrs apart**: Al^{3+}, Ca^{2+}, Fe^{2+}, Mg^{2+} supplements; cholestyramine; chromium; ciprofloxacin; colestipol; colesevelam; orlistat; sevelamer; simethicone; sodium polystyrene (can test for % absorption). • **Space 8-12hrs:** raloxifene 12hrs, sucralfate 8hrs • **↓ Level**: ? H_2 blockers & PPI's due to ↑gastric pH, estrogens, soy; inducers concern if intermittent dosing eg. carbamazepine, phenobarb, phenytoin, rifampin • **↑ Effect**: SSRI, TCAs ↑ receptor sensitivity to catecholamines **M**: TSH during maintenance tx q6-**12**months (draw blood in **am**) **Precautions**: CVD, ↓BMD, DM, Elderly ↑CV effects	Individualize dose based on pts symptoms 50, 75, 100, 112ug po daily **Young, healthy**: 1.6 µg/kg/day (Ideal Body Wt) • Full replacement dose • 60kg$_{x\ 1.6ug/kg/d}$=100µg/d; 70kg$_{x1.6ug/kg/d}$=112µg/d • TFTs 6-8 weeks **2-3 weeks if severe** • ↑by 12.5-25 µg **until normal TSH & ↓S&S** **Also see Special Population Considerations column** • Euthyroid quicker with **weight based dosing** vs slow titration, but sx's & quality of life improve at same rate • Few pts require >200 µg/day. If TSH remains elevated query compliance & absorption. • 6-8 weeks before ↑dosage as LT4 has long t1/2 • **Dose same time each day! in AM** 30-60 mins before breakfast **or HS 4hr** after supper • Entire dose may be given once weekly if non-compliant.	$9-11
Liothyronine (LT3) CYTOMEL ✗ ⊗ **5, 25 µg tablet** P L **(LT3 25 µg = LT4 100 µg)**	**Not 1st line alone or in combo with LT4 for hypothyroidism** • Simple (nontoxic) goiter - may be tried to ↓ size of goiter • T_3 suppression test differentiate hyperthyroidism from euthyroidism • Thyroid Carcinoma radioimaging →may replace T4 due to rapid clearance which allows for sooner radioimaging without hypothyroid sx • Refractory depression: possible augmentation limited evidence **Pregnancy**: LT4 is preferred over LT3 in pregnancy. • **ATA 2011** – strongly recommends LT3 **NOT** be used.	**AE**: symptoms of hyperthyroidism if overtreated, ↑ incidence of **cardiac events** compared to LT4 **Pharmacokinetics:** • **Peak effect**: 1-2 hours; **$t_{1/2}$**: 1.5 days; **Absorption**: 95-100% • Rapid absorption & short $t_{1/2}$ vs LT4 leads to marked **fluctuations** in T3 levels & S&S. **Combination Therapy: trials of LT4 vs. LT4/LT3 combo have shown no benefit for combination therapy**	*Mild Hypothyroidism* • Initially 25 µg po daily • ↑ by 12.5-25 µg q1-2 weeks. • Maintenance dosage = 25-75 µg daily • Titration of dose harder than LT4; but if intolerant to LT4, patient may tolerate LT3	$45-125
Desiccated Thyroid THYROID **30, 60, 125mg tab** **60 mg = LT4 100 µg or LT3 25 µg**	• T3 & T4 from **porcine** thyroid glands • **Guidelines suggest should be avoided** • No randomized trials compared with LT4 or LT4/LT3 P L	**AE**: symptoms of hyperthyroidism if overtreated, animal protein derived → antigenic in allergic or sensitive pts • Unpredicatable stability & batch variation	Initial dose: 60 to 300 mg daily. Maintenance dose: 30-125 mg daily	$12-16
THIONAMIDES FOR HYPERTHYROIDISM – inhibits T4 conversion to T3				
Methimazole (MMI) TAPAZOLE **5mg^{ς} (10mg$^{✗▼}$) tablet** **MMI ~10x more potent than PTU** P_1,P_{2-3} L *Can be given rectally if necessary*	**MMI 1st choice for Tx of hyperthyroidism** adults & kids • **Clinical** Response → **days; Lab** Response **4-6 weeks**. • RAI: If MMI used pre, may need to resume post RAI until sx normal. • **Block-replace regimen** high dose thionamide + T4 **not indicated →↑AEs.** **Pregnancy**: caution in 1st trimester craniofacial malformations. Alternative if PTU AE. MMI preferred over PTU for 2nd & 3rd trimester. Dose often less in 2nd & 3rd trimester. **Breastfeeding**: Caution if >10mg/d. **ATA 2011**:20-30mg/d safe. **Pharmacokinetics: Peak** effect: **0.5-1**hr; **$t_{1/2}$**: 4-6hr; **Absorption**: 93% **? effect of food** ; not protein bound; renal excretion; CYP450 metabolism no active metabolites	**AE**: **Serious (rare): agranulocytosis** 0.1-0.5% of pts; possibly more with PTU (baseline WBC regular CBC not cost effective, pt to monitor for S&S fever, sore throat, mouth ulcers), neutropenia same maybe with PTU → **refer**, **Reversible cholestatic** jaundice: if D/C→slow complete recovery (occurs usually in first 3 months incidence 1.3%) Lupus like vasculitis **Minor** may subside with continued use > 4 wks: skin rash if persistent use antihistamine or topical steroid, arthralgias, abnormal taste/smell **CI**: thionamide allergy **DI**: **Warfarin** may ↓INR; **Digoxin** ↑dig level; **2D6** inhibitor→ DI with TCA, codeine, paroxetine; **RAI** impair uptake & ↓ efficacy **M**: TSH; CBC & LFT: baseline & at 1wk (see AE monitoring above) **Precautions**: bleeding disorders or easy bruising, liver dx, S&S of infection fever, headache, malaise, skin eruptions, sore throat, surgery	*Mild hyperthyroidism* 10-15 mg daily initially; 5-15 mg daily maintenance *Mod-severe hyperthyroidism* 20-30 mg daily initially; 5-15 mg daily maintenance *Severe hyperthyroidism-large goitres* 30-40 mg daily initially; 5-15 mg daily maintenance • Initially divided doses to ↓ GI upset • Max blocking dose = 60-120 mg/day • ↑dose if no improvement in TSH & T4 levels in 4–6 weeks. • No dosage adjustment in elderly *Pediatric hyperthyroidism* Initial= 0.4-0.7 mg/kg/day ÷ q 8-12 hours Maintenance= 0.2 mg/kg/day ÷ q 8-12 hours	$15-35 Formulary: not covered by some.
Propylthiouracil (PTU) PROPYL- THYRACIL **50,100mg tablet^{ς}** P_1,P_{2-3} L *Can be given rectally as an enema or suppository* **↑liver failure** 0.1-0.2%: ? restricting PTU to pt with toxic reaction to MMI where RAI/surgery not an option	Preferred for **Thyroid Storm** (↓ peripheral conversion T4→T3) • Use PTU only in pts who have an allergy/intolerance to MMI, have thyroid storm or are in 1st trimester of pregnancy. • **Clinical** Response → **days; Lab** Response **4-6 weeks.** • RAI: If PTU used pre, may need to resume post RAI until sx normal. • **Block-replace regimen** high dose thionamide + T4 **not indicated →↑AEs.** **Pregnancy**: PTU preferred for 1st trimester. Consider MMI for 2nd & 3rd trimester (PTU risk of maternal hepatotoxicity). Dose often less in 2nd & 3rd trimester. **Breastfeeding**: caution if >200mg/d. **ATA 2011**: <300mg/d safe. **Pharmacokinetics: Peak** effect: **0.5-1.5** hr; **$t_{1/2}$**: 1-2hr; **Absorption**: 75% food no effect Protein bound **~75%**; Liver metabolism; Renal excretion	**AE**: **Serious (rare): agranulocytosis** 0.1-0.5% of pts (baseline WBC regular CBC not cost effective, pt to monitor for S&S fever, sore throat, mouth ulcers); neutropenia same maybe with MMI → **refer**; **severe liver 0.1% , hepatitis with hepatocellular injury** (liver transplants 3rd most common drug cause, d/c PTU immediately if S&S); Lupus like vasculitis **Minor** may subside with continued use > 4 wks: skin rash if persistent use antihistamine or topical steroid, arthralgias, GI upset divide dose **CI**: liver dx (S&S fatigue, weakness, abdominal pain, itching, easy bruising, yellowing of the eyes/skin), thionamide allergy **DI**: **Warfarin** may ↓INR; **Digoxin** ↑dig level ; **RAI** impair uptake & ↓ efficacy **M**: TSH; CBC & LFT: baseline & at 1wk signs of liver dx esp. during 1st 6months (see AE monitoring above) **Precautions**: thrombocytopenia, aplastic anemia	*Graves' Disease* *Initial*= 300mg/day divided q8h max. 900–1200 mg/day *Maintenance*=100–150mg/day divided q8–12h • For doses >300 mg = divide dose • If no improvement after 4–6 wks ↑ dose. • Once euthyroid, ↓dose gradually q4–6 wks to the lowest effective dose *Thyroid Storm* 600–1200 mg/day divided every 4–6 hours • As sx resolve, slowly ↓dose to maintenance dose *Avoid generally in Children*: hepatotoxicity *Pregnancy* **Initial**= full PTU dose, monitor TFTs monthly. **Stable**= Use lowest effective dose.	$20-35

LIOTRIX (LT4 & LT3 in 4:1 ratio) available in the USA. OTC preparations (Thyroid American Biologics; Thyroid Complex The Vitamin Shoppe) have not been evaluated by Health Canada (some concern → may contain unregulated animal products).

ς=scored tab **✗**=Non-formulary Sask ☎=Exception Drug Status Sask. **⊗**=not covered by NIHB **▼**=covered by NIHB **Δ**=changes **♀**=female **♂**=male **1°**=primary **2°**=secondary **AAP**=American Academy of Pediatrics **AE**=adverse events **AF**=atrial fibrillation **anti-TPO**= antithyroid peroxidase antibody **ATA**=American Thyroid Assoc. **BMD**=bone mineral density **BMR**=basal metabolic rate **BP**=blood pressure **CBC**=complete blood count **CHD**=coronary heart dx **CVD**=cardiovascular dx **CV**=cardiovascular **d/c**=discontinue **DM**=diabetes mellitus **dx**=diagnosis/disease **ECG**=electrocardiogram **FNAB**=fine needle aspiration biopsy **FT3**=free triiodothyronine **FT4**=free thyroxine **HF**=heart failure **HR**=heart rate **HTN**=hypertension **hx**=history **I**=iodine **LFT**=liver function tests **LT4**=levothyroxine **MI**=myocardial infarction **MMI**=methimazole **mos**=months **pt**=patient **PTU**=propylthiouracil **RAI**=radioactive iodine **RAIU**=radioactive iodine uptake **S&S**=signs & symptoms **sx**=symptom **T1DM**=Type 1 DM **$t_{1/2}$**=half life **FT3**=free triiodothyronine **TCA**=tricyclic antidepressant **TFT**=Thyroid Function Tests (TSH/FT4/FT3) **TRAbs**=thyroid receptor antibodies **TSH**=thyroid stimulating hormone **Tx**=treatment **ULN**=upper limit of normal **wks**=weeks **wt**=weight.

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FDA Propylthiouracil-Induced Liver Failure June/09 FDA has identified 32 AERS cases (22 adult and 10 pediatric) of serious liver injury associated with propylthiouracil use. Of the adult cases, 12 deaths and 5 liver transplants occurred. Among the pediatric patients, 1 case resulted in death and 6 in liver transplants. In contrast, for methimazole 5 AERS cases of serious liver injury were identified. All five cases were in adult patients and 3 resulted in death. (**April 21, 2010**: Propylthiouracil: FDA has added a Boxed Warning to the label for propylthiouracil, to include information about reports of severe liver injury and acute liver failure, some of which have been fatal, in adult and pediatric patients using this medication. A boxed warning has been added to the hyperthyroidism drug propylthiouracil (PTU) to alert clinicians about the drug's risk for severe liver injury, the FDA announced on Wednesday. The new labeling is based in part on postmarketing safety reports of severe liver injury — including 15 deaths — in 23 adult and 11 pediatric patients taking PTU. A warning about the potential dangers of the drug was issued by the agency last June. The FDA recommends that PTU only be used in patients who cannot tolerate methimazole or other treatments for hyperthyroidism and in women just before and during their first trimester of pregnancy. Patients will now receive a medication guide upon filling a prescription for PTU. FDA drug safety communication)

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Given these potential adverse effects, the FDA issued an alert on June 4, 2009 that noted the risk of serious liver injury, including liver failure and death, with the use of PTU in adult (1:10,000) and pediatric (1:2,000) patients. These conferences focused on the relative safety of methimazole compared with PTU.[11-14,16] Approximately 30% of patients treated with PTU will have 1- to 2-fold elevations of serum aminotransferase levels. The liver disease associated with PTU can be severe. In the Adverse Event Reporting System (AERS), approximately 22 adult (12 deaths, 5 hepatic transplants) and 10 pediatric (1 death, 6 hepatic transplants) cases of serious hepatic injury associated with PTU treatment were reported. Methimazole, by contrast, was associated with 5 adult cases of serious hepatic injury with 3 deaths. In a system that may overlap with AERS, the United Network for Organ Sharing reported 23 hepatic transplants from 1990 to 2007 (16 adult, 7 children) related to PTU-associated hepatic failure.[11-13,16] Concurrently, no liver transplants related to the use of methimazole were reported. The average PTU dose in children and adults requiring liver transplant was 300 mg daily. Liver failure occurred between 6 and 450 days after starting treatment (median 120 days). Furthermore, there were 2 reports of serious maternal liver disease during pregnancy and 2 reports of liver injury in fetuses of mothers who ingested PTU during pregnancy.[11-14,16]

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