



Indian Health Service
National Pharmacy and Therapeutics Committee
Formulary Brief: Hyperthyroidism
-January 2021-



Background:

The management of hyperthyroidism was reviewed during the Winter 2021 meeting of the IHS National Pharmacy and Therapeutics Committee (NPTC). After consideration of current treatment guidelines, as well as clinical safety, efficacy and utilization data regarding the use of thionamides to achieve euthyroidism, the NPTC voted to **ADD methimazole and propylthiouracil to the NCF**.

Discussion:

Hyperthyroidism is defined by a group of clinical and laboratory abnormalities caused by supra-physiologic synthesis and release of thyroid hormone from the thyroid gland, distinct from the less common group of extra-thyroidal conditions leading to thyrotoxicosis (e.g., exogenous thyroid hormone ingestion or metastatic differentiated thyroid cancer). The most common cause of hyperthyroidism in developed countries is Graves' disease, followed by toxic multinodular goiter, toxic adenoma and thyroiditis¹.

Unrecognized or uncontrolled hyperthyroidism is associated with a range of adverse effects, including atrial fibrillation, osteoporosis, and congestive heart failure. Graves' ophthalmopathy can be a vision-threatening and stigmatizing physical deformity. Thyroid storm, precipitated often by infection, pregnancy, or trauma, constitutes a medical emergency for which mortality remains >10% in the developed world.^{1,2} Consequences of poor control of hyperthyroidism in pregnancy can include congestive heart failure and severe preeclampsia, as well as fetal growth restriction and thyroid dysfunction.^{3,4}

Subclinical hyperthyroidism is present when thyroid-stimulating hormone (TSH) is below the normal range but free T4 and total T3 are normal. It is associated with increased risk for congestive heart failure, osteoporosis, mortality, and atrial fibrillation, especially in older patients with TSH values < 0.1 mU/L.¹ Though there is some controversy regarding optimal treatment given the absence of evidence showing improvement, the American Thyroid Association 2016 Guideline suggests treating persons ≥65 years of age with persistent TSH <0.1 mU/L and other adults with specific risk factors for heart disease or osteoporosis.^{5,6}

Modalities for definitive treatment of hyperthyroidism, generally with the goal of permanent remission, include radioiodine (RAI) ablation of the thyroid, surgical thyroidectomy, or a thionamide medication.

Thionamides have been the mainstay for pharmacologic suppression of thyroid overactivity since their introduction in the late 1940s. Methimazole (MMI) is preferred for most non-pregnant adults and children, due to the risk of more severe hepatic injury with propylthiouracil (PTU), for which the FDA added a boxed warning in 2010.¹⁴ PTU is reserved for use in the first trimester of pregnancy due to concern about the spectrum of more severe birth defects associated with MMI, including choanal and esophageal atresia, aplasia cutis, and others. Agranulocytosis is a serious but uncommon adverse reaction with either drug, seen more often with higher doses and within the first 90 days of therapy.⁷ In Europe, MMI - rather than thyroidectomy or RAI - is the mainstay of treatment for Graves' disease in young children given higher rates of spontaneous remission seen after puberty and remaining safety concerns around the use of RAI in early childhood.⁸

In Graves' autoimmune and autonomous nodular disease, MMI is commonly used in the United States to achieve euthyroidism prior to definitive treatment with RAI.⁵ Historically the treatment of choice for Graves' disease, use of RAI, appears to have declined in recent decades in favor of longer-term use of thionamides, largely due to concern that increases in post-radiation TSH receptor antibody levels may continue to contribute to development or worsening of Graves ophthalmopathy.⁹ Remission of Graves' autoimmunity can occur in 30-50% of patients after 12-18 months of MMI treatment and RAI may be used contingent on failure of this strategy or later relapse.^{5,9} Some patients may prefer long-term treatment with low-dose MMI, which can be a safe alternative.^{8,10}

A Cochrane review of 2 RCTs of 214 Graves patients assigned either to RAI or MMI concluded that RAI was associated with development or worsening of Graves ophthalmopathy with a RR of 1.94 (95% CI 1.40 to 2.70) but was less often associated with disease relapse, RR 0.20 (95% CI 0.01 to 2.66).¹¹ A 2013 network meta-analysis also showed that patients treated with a thionamide were more likely to relapse than those treated with RAI (OR 6.25, 95% CI 2.40 to 16.67) or surgery (OR = 9.09, 95% CI, 4.65-19.23).¹² Given that treatment recommended by clinicians for definitive treatment of Graves' will generally result in permanent hypothyroidism, shared informed decision making is important to square the rationale for a this with a patient's values and preferences. Counseling for smoking cessation is strongly encouraged, particularly if RAI is chosen.⁹

Thyroidectomy may be performed for definitive management of Graves' disease by a high-volume thyroid surgeon,¹³ particularly where there is a concern that moderate to severe Graves ophthalmopathy may be worsened by RAI treatment; for refractory amiodarone-induced thyrotoxicosis; >6 months prior to intended conception; and in the second trimester of pregnancy when a thionamide does not provide adequate control or is not tolerated by the patient.⁵

Findings:

Hyperthyroidism is a relatively uncommon but important cause of morbidity in young to older middle-age adults. Surgery and RAI ablation are considered the most definitive therapy. Pharmacologic suppression of thyroid gland activity using methimazole or propylthiouracil has for many decades been an irreplaceable component in management of thyroid storm, as well as in Graves' disease where treatment can lead to remission in up to half of patients. Graves' disease disproportionately affects women in their child-bearing years where detrimental effects of untreated thyrotoxicosis in pregnancy are well established. Long-term low-dose maintenance use can be safe in selected cases.

If you have any questions regarding this document, please contact the NPTC at IHSNPTC1@ihs.gov. For more information about the NPTC, please visit the [NPTC website](#).

References:

1. Park P, Braunstein G. Hyperthyroidism, amended 2019 July 8, cited 2021, Jan 18. In Essential Evidence Plus [Internet]. John Wiley & Sons, Inc. c2021.
2. Ono Y, Ono S, Yasunaga H, et al. [Factors associated with mortality of thyroid storm: analysis using a national inpatient database in Japan](#). *Medicine (Baltimore)*. 2016; 95(7): e2848.
3. Tonacchera M, Chiovato L, Bartalena L, et.al. [Treatment of Graves' hyperthyroidism with thionamides: a position paper on indications and safety in pregnancy](#). *J Endocrinol Invest*. 2020;43(2):257-265.
4. American College of Gynecology. [Thyroid Disease in Pregnancy: ACOG Practice Bulletin, Number 223](#). *Obstet Gynecol*. 2020 Jun;135(6):e261-e274.
5. Ross D, Burch H, Cooper D, et al. [2016 American Thyroid Association Guidelines for Diagnosis and Management of Hyperthyroidism and Other Causes of Thyrotoxicosis](#). *Thyroid*. 2016; 26(10):1343-1421.
6. Papadopoulou AM, Bakogiannis N, Skrapari I, et al. [Thyroid Dysfunction and Atherosclerosis: A Systematic Review](#). *In Vivo*. 2020; 34(6):3127-3136.
7. Ross D. Thionamides: Side effects and toxicities. UpToDate, Cooper D (ed.), UpToDate, Waltham, MA (accessed 1/10/2021).
8. Kahaly G, Bartalena L, Hegedus L, et al. [2019 European Thyroid Association Guideline for the Management of Graves Hyperthyroidism](#). *European Thyroid Journal*. 2018; 7:167-186.
9. Kahaly GJ. [Management of Graves Thyroidal and Extrathyroidal Disease: An Update](#). *J Clin Endocrinol Metab*. 2020; 105(12):3704-20.
10. Azizi F. [Long-Term Treatment of Hyperthyroidism with Antithyroid Drugs: 35 Years of Personal Clinical Experience](#). *Thyroid*. 2020;30(10):1451-1457.
11. Ma C, Xie J, Wang H, et al. [RAI therapy versus antithyroid medications for Graves' disease](#). *Cochrane Database of Syst Rev*. 2016, Issue 2. Art. No.:CD010094.
12. Sundaresh V, Brito J, Wang Z, et al. [Comparative effectiveness of therapies for Graves hyperthyroidism: A systematic review and network meta-analysis](#). *J Clin Endocrinol Metab*, 2013; 98(9):3671-3677.
13. Sosa JA, Bowman HM, Tielsch JM, et.al. [The importance of surgeon experience for clinical and economic outcomes from thyroidectomy](#). *Ann Surg*. 1998; 228:320-330.
14. U.S. Food and Drug Administration. [FDA Drug Safety Announcement: New Boxed Warning on severe liver injury with propylthiouracil](#). April 21, 2010.