Hyperthyroidism is a common endocrine disorder. A recent national survey found a prevalence of 0.5% in the general US population.3 The most common cause of hyperthyroidism is Graves’ disease, accounting for 80% to 90% of cases. Three treatment options currently are available for patients with Graves’ disease: radioiodine therapy, antithyroid drugs, and thyroidectomy. The clinician should choose among these options based on an assessment of the patient’s condition, the physician’s experience with each option, and the patient’s preference. In the United States, radioiodine therapy (131I) is the most frequently chosen treatment option in Graves’ disease, but antithyroid drugs usually are prescribed for younger patients and for pregnant or lactating women. Antithyroid drugs are used in the hope that the patient will achieve a remission after 12 to 24 months of therapy. Antithyroid drug therapy is rarely lifelong, and the remissions achieved are possibly due to a waning of the autoimmune process related to the immunosuppressive effects of the drug. Clinicians must be well versed in this treatment option in order to select patients for primary antithyroid drug therapy, choose an antithyroid agent, determine the optimal duration of treatment and drug dosage, and decide whether to use antithyroid drugs before and/or after radioiodine therapy.

Type of Available Evidence: Randomized controlled trials, prospective cohort studies, retrospective studies, and expert opinion.

Grade of Available Evidence: Good; but varies for different conclusions.

Conclusion: In general, patients having relatively mild Graves’ disease, pregnant women, and children are the best candidates for primary antithyroid therapy. Methimazole is, with a few exceptions, the preferred drug in the management of hyperthyroidism due to Graves’ disease. Propylthiouracil is preferred in thyroid storm, pregnancy, and lactation. Selection of the correct initial antithyroid drug dose requires clinical experience and judgment in order to strike a balance between the risk of side effects and hypothyroidism, and the ability to normalize the thyroid function. Controlled trials have shown that the optimal duration of antithyroid therapy is about 12 to 18 months.
lactating women. Surgery seldom is recommended and is reserved for patients with very large goiters, or for situations in which radioiodine therapy is contraindicated or refused by the patient.2

Antithyroid drugs act primarily to inhibit thyroid hormone synthesis within the thyroid gland by interfering with thyroid peroxidase-mediated utilization of iodine. In addition, antithyroid drugs have a putative effect on the immune system that may help account for the remissions that are achieved in some patients. Propylthiouracil (PTU), in particular, inhibits the peripheral conversion of thyroxine (T4) to triiodothyronine (T3). However, this is a relatively weak effect and of questionable clinical relevance, except perhaps in patients with thyroid storm (to be discussed further on).

Some of the most common issues faced by clinicians when using antithyroid drugs to treat Graves’ disease include appropriate patient selection for primary antithyroid drug therapy; choosing an antithyroid agent; determining the optimal duration of treatment and drug dosage; and making the decision to use antithyroid drugs before and/or after radioiodine therapy.

**Patient Selection for Primary Antithyroid Drug Therapy**

In general, antithyroid drugs are used as primary treatment of hyperthyroidism in the hope that patients will achieve remission after 12 to 24 months of therapy. Antithyroid drug therapy rarely is lifelong, and the remissions achieved are due possibly to a waning of the autoimmune process that may be related to immunosuppressive effects of the drug. Numerous retrospective studies have shown higher remission rates in patients with relatively small goiters, those whose thyroid function tests are only slightly deranged, and those with low or undetectable circulating anti-thyroid-stimulating hormone receptor antibodies (TSAb) at baseline.3 All these findings are associated with milder Graves’ disease, but none have a high enough sensitivity or specificity to be useful in choosing therapy for individual patients. For example, in one large randomized trial,4 no single baseline clinical factor could predict success or failure of antithyroid drugs in achieving remission after 12 months of therapy and a 4-year follow-up. Nevertheless, primary antithyroid drug therapy would be a reasonable choice for individuals with mild disease. Patients with large goiters and severe biochemical derangements of thyroid function, especially a very high serum T3 level (>600 ng/dL),5 are less likely to achieve remission and are therefore less satisfactory candidates for primary drug treatment. For this latter group, early radioiodine therapy is the preferred option.

The decision to choose antithyroid drugs over radioiodine as the primary treatment must take into account patient preference as much as physician experience and judgment. In a recent trial patients with Graves’ disease were prospectively randomized to receive antithyroid drug therapy, radioiodine therapy, or surgery as primary treatment; patient satisfaction was equally high for all 3 treatments.6 Furthermore, antithyroid drug treatment was equally cost effective to radioiodine treatment.7

Antithyroid drugs remain the preferred treatment for children and adolescents with Graves’ disease, although radioiodine is now more often used because of diminishing concerns about subsequent malignancy.8 Antithyroid drugs also are the treatment of choice in pregnant women with hyperthyroidism, since radioiodine treatment is contraindicated in this group and surgery poses unnecessary risk to the fetus.

**Choice of Antithyroid Agent**

The 2 available antithyroid drugs in the United States are PTU and methimazole (MMI). In choosing which to use, one must strike a balance among several factors, including efficacy, toxicity, cost, compliance, and influence on subsequent radioiodine therapy.

**Deciding Which Drug Has Greater Efficacy**

Analyzed retrospective studies and randomized prospective trials of patients with Graves’ disease show that MMI (typically administered in a ratio by weight of 1:10 to PTU) is more effective than PTU in inducing euthyroidism.9,10 However, clinical experience suggests that this commonly accepted potency ratio between the 2 drugs is an underestimate. A true MMI-to-PTU potency ratio seems closer to 30:1, as some patients can be well controlled with relatively small doses of MMI (eg, 5-10 mg daily).11,12 In the instance of thyroid storm, however, PTU historically has been preferred to MMI due to its additional inhibitory effect on peripheral T4-to-T3 conversion, although no randomized studies have compared the 2 drugs in this situation.

**Considerations Regarding Drug Toxicity**

Both antithyroid drugs can cause minor adverse reactions including skin rash (urticarial or macular), arthralgias, fever, and gastrointestinal intolerance. Data on antithyroid drug toxicity in patients with Graves’ disease, amassed from retrospective and prospective series, have shown little difference between the 2 drugs in overall frequency of side effects,13-16 including minor side effects (which generally occurred in 5% to 15% of patients) and major side effects (which occurred in approximately 0.5% of patients).17,18 Most reports have concluded that side effects are dose related for MMI19-21 and possibly for PTU, as well.19,16

Both antithyroid drugs may cause major adverse reactions, particularly agranulocytosis, hepatitis, and vasculitis (Table 1). Agranulocytosis may present with...
oropharyngeal infection and/or pneumonia. It mandates drug discontinuation, hospitalization, antibiotics, and potentially granulocyte colony-stimulating factor (G-CSF). Agranulocytosis rarely has been reported in patients taking less than 15 mg of MMI per day, whereas it has been reported in patients taking even the lowest effective dose of PTU. Drug-induced toxic hepatitis and antineutrophil cytoplasmic antibody (ANCA)-positive vasculitis are rare and seen almost exclusively in patients taking PTU. Thirty percent of patients treated with PTU develop a transient, asymptomatic increase in transaminases after 2 months of therapy. Though rare, immunooallergic hepatitis seen with PTU can be fulminant, even fatal. Development of symptomatic vasculitis presents with fever, palpable purpura, renal dysfunction (ranging from proteinuria to rapidly progressive renal failure), hemoptysis, myalgias, lupuslike syndrome, and Raynaud’s phenomenon. Drug cessation is mandatory in such cases.

<table>
<thead>
<tr>
<th>Table 1. Methimazole vs Propylthiouracil in the Treatment of Hyperthyroidism Secondary to Graves’ Disease</th>
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</thead>
<tbody>
<tr>
<td><strong>MMI</strong></td>
</tr>
<tr>
<td><strong>Efficacy</strong></td>
</tr>
<tr>
<td><strong>Compliance</strong></td>
</tr>
<tr>
<td><strong>Cost</strong></td>
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<tr>
<td><strong>Effect on ¹³¹I (radioiodine) therapy</strong></td>
</tr>
<tr>
<td><strong>Toxicity to dose relation</strong></td>
</tr>
<tr>
<td><strong>Side Effects</strong></td>
</tr>
<tr>
<td>Agranulocytosis</td>
</tr>
<tr>
<td>Hepatitis</td>
</tr>
<tr>
<td>ANCA-positive vasculitis</td>
</tr>
<tr>
<td>Antithyroid arthritis syndrome</td>
</tr>
<tr>
<td>Hypoprothrombinemia</td>
</tr>
<tr>
<td>Insulin autoimmune syndrome</td>
</tr>
<tr>
<td>Minor side effects</td>
</tr>
</tbody>
</table>

and high doses of glucocorticoids and/or cyclophosphamide may be required.29 Interestingly, a large cross-sectional study suggests that some patients with Graves’ disease are ANCA-positive even before treatment is instituted.25 Furthermore, the majority of patients who became ANCA-positive due to use of antithyroid drugs (15% to 30%) remained asymptomatic.25 In summary, it appears that MMI generally is a safer drug than PTU, especially at a dose of 15 mg per day, which is adequate for many patients with mild to moderate Graves’ disease. In pregnancy, however, PTU is the preferred antithyroid drug in the United States because MMI rarely has been associated with aplasia cutis, a skin defect most commonly occurring in the scalp of the fetus as well as more severe fetal malformations, including choanal atresia, tracheal-esophageal fistulae, hypoplastic nipples, and facial anomalies. In contrast, PTU is not known to be teratogenic. Both drugs are equally capable of causing transient fetal hypothyroidism if taken in excessive dosage. PTU also may be the preferred choice during lactation because smaller quantities of PTU are excreted in breast milk,27 although both drugs are approved by the American Academy of Pediatrics for use in nursing mothers.28

**Cost Analysis**

The cost of antithyroid medication varies widely depending on retailer and brand. Out-of-pocket expenses vary additionally with one’s prescription plan. Prescribed at the usual ratio (MMI-to-PTU, 1:10), MMI is more expensive than PTU ($43/month for a daily dose of MMI 30 mg compared with $26/month for a daily dose of PTU 300 mg, according to www.destinationrx.com), but when administered at a ratio closer to equipotency (MMI-to-PTU, 1:30), MMI becomes the less costly choice ($15/month for a daily dose of MMI 10 mg compared with $26/month for a daily dose of PTU 300 mg).

**Compliance Considerations**

Because Graves’ disease may cause poor concentration and memory impairment, one could hypothesize that compliance rates would be especially poor in patients with hyperthyroidism. Therefore, a drug that can be given in a single daily dose would be preferred. Since the serum half-life and duration of action of MMI is longer (t1/2 = 4-6 h) than that of PTU (t1/2 = 60 min),29,30 MMI can be given as a single daily dose to most patients, whereas PTU generally must be given every 6 to 8 hours, at least initially. Ease of administration logically translates into improved compliance. In the only prospective randomized trial looking at compliance, the compliance rate (defined as taking 80% of prescribed pills) was significantly higher for MMI (83%) than for PTU (53%).29

**Influence on the Efficacy of Radioiodine Therapy**

Another reason to prefer one antithyroid drug to another would be any putative effect on the outcome of subsequent radioiodine therapy. Antithyroid drugs generally are used in 2 contexts. As primary treatment for hyperthyroidism secondary to Graves’ disease, they usually are administered for 12 to 24 months and then discontinued to see if the patient experiences remission. In the 50% to 60% of such patients who relapse, radioiodine almost always is selected as the next therapeutic step. In a second scenario, antithyroid drugs are given for a short-term (2- to 3-month) period to “prepare” patients for radioiodine therapy. In particular, pretreatment with an antithyroid drug before radioiodine therapy is recommended for elderly patients or those with heart disease.21 Occasionally, during the weeks following radioiodine therapy, some patients experience a transient increase in thyroid hormone levels, which is possibly due to radiation-related thyroiditis or a rise in TSAb following injury to the thyroid. It has been theorized that normalization of thyroid function prior to radioiodine treatment would limit any potential worsening of thyroid function following radioiodine administration. Recent prospective studies suggest that antithyroid drugs may attenuate the rise in thyroid function that occasionally occurs following radioiodine treatment.22 However, this also may have a downside, since it has been generally thought that antithyroid drugs may negatively affect the efficacy of subsequent radioiodine therapy. Retrospective20 and prospective21,22 studies have shown that PTU significantly decreases the success rate of subsequent radioiodine treatment (Figure 1), but a similar effect for MMI in prospective trials has not been observed (Figure 2).21,33,34 Since a large number of patients treated with antithyroid agents eventually receive radioiodine, the absence of any effect of MMI on the outcome of ablative therapy is a decided advantage. There are few data on the effects of antithyroid drugs on radioiodine efficacy when used after radioiodine treatment. Limited data suggest an adverse effect of PTU on cure rates,23 whereas MMI seems to have no consistent effect on the outcome of radioiodine treatment.26

Based on the available data, MMI seems to be the drug of choice for most patients with hyperthyroidism due to its greater efficacy, lower toxicity at low doses, better compliance profile, and lack of adverse effect on subsequent radioiodine therapy (Table 1). However, PTU remains the drug of choice for the treatment of thyroid storm and for pregnant or lactating women with Graves’ disease.

**Choice of Initial Antithyroid Drug Dose**

The initial dosages of antithyroid drugs need not be adjusted for age, body weight, or renal or liver func-
Although antithyroid drugs may have immunosuppressive effects, there is no evidence that higher initial drug doses improve the prospects of a patient achieving a remission. Therefore, the dose of drug that is used initially should be based on the clinical circumstances.

In general, MMI dosages of 20 to 40 mg daily and PTU 400 to 600 mg daily are appropriate for patients with severe disease (baseline free T4 levels >2 to 3 × the upper limit of normal, baseline T3 levels >3 to 4 × the upper limit of normal). On the other hand, 10 to 20 mg of MMI or 200 to 300 mg of PTU daily usually are sufficient starting dosages in most patients with milder disease.

A recent prospective study showed that higher doses of MMI normalize thyroid function faster than do lower doses, but at the cost of more frequent adverse reactions. However, it should be noted that since antithyroid drugs do not inhibit the release of preformed thyroid hormone, thyroid function improves gradually even if large doses are used. For example, in the above-mentioned study, 68% of patients taking MMI 10 mg daily were euthyroid within 3 weeks, vs 83% of patients receiving 40 mg daily (P < .01). At 6 weeks, however, the percentages were 85% and 92%, respectively (P < .01). Thus, high-dose treatment will normalize thyroid function faster in some patients, but the differences become smaller after a longer duration of treatment. Further, as noted above, the risk of side effects with MMI increases with higher doses of the drug, a factor that must be taken into account, as well.

Finally, it is important to note that drug-induced hypothyroidism also is a risk when the dose of drug is too high for the patient’s degree of thyrotoxicosis. In one prospective study, iatrogenic hypothyroidism occurred in 50% of patients within 4 weeks of receiving a dose of antithyroid drug inappropriately large for their degree of hyperthyroidism.

### Establishing Treatment Duration

Retrospective studies have suggested that the longer a patient takes an antithyroid drug, the greater the likelihood is that patient will achieve remission. However, this does not take into account the natural rate of remission that might occur without drug therapy. In fact, prospective studies have not confirmed this impression. One prospective randomized trial did find that patients with Graves’ disease who were treated for 18 months had a lower relapse rate than those treated for 6 months only. However, another study found no significant difference between a 6-month and a 12-month “block-replace” regimen, in which thyroxine was added for those patients who become hypothyroid on the antithyroid drug. In another prospective randomized trial, the remission rate was no higher in patients receiving antithyroid drugs for 24 months compared with those who received treatment for 12 months only. Additionally, a subsequent study found similar remission rates in patients receiving treatment for 18 months compared with those treated for 42 months. The results of these studies are summarized in Table 2. It seems reasonable that patients be treated for 12 to 18 months, in accordance with a recent evidence-based systematic review of the literature.

After 12 to 18 months, antithyroid medication should be discontinued or, perhaps more prudently, tapered, and the patient should be observed for remission/relapse. In general, relapses are more likely to occur within the first 3 to 6 months of stopping the
Table 2. Relapse Rates Following Antithyroid Treatment of Different Durations

<table>
<thead>
<tr>
<th>Study</th>
<th>Shorter Treatment</th>
<th>Relapse Rate</th>
<th>Longer Treatment</th>
<th>Relapse Rate</th>
<th>Evaluation/ Follow-up</th>
<th>Difference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Allannic et al⁴⁵</td>
<td>6 months</td>
<td>58%</td>
<td>18 months</td>
<td>38%</td>
<td>1 year</td>
<td>Significant</td>
</tr>
<tr>
<td>Weetman et al⁴⁶</td>
<td>6 months</td>
<td>41%</td>
<td>12 months</td>
<td>35%</td>
<td>1 year</td>
<td>Not significant</td>
</tr>
<tr>
<td>Garcia-Mayor et al⁴⁷</td>
<td>12 months</td>
<td>46%</td>
<td>24 months</td>
<td>54%</td>
<td>2 years</td>
<td>Not significant</td>
</tr>
<tr>
<td>Maugendre et al⁴⁸</td>
<td>18 months</td>
<td>36%</td>
<td>42 months</td>
<td>29%</td>
<td>2 years</td>
<td>Not significant</td>
</tr>
</tbody>
</table>

antithyroid drug. Thereafter, relapses occur at a slower rate, and ultimately plateau after several years, contributing to an overall relapse rate of approximately 50% to 60%.⁶ If a relapse occurs, consideration should be given to definitive radioiodine therapy.⁷

CONCLUSION
In general, patients having relatively mild disease, pregnant women, and children are the best candidates for primary therapy with antithyroid medication. With a few exceptions, MMI is the preferred antithyroid drug in the management of hyperthyroidism secondary to Graves’ disease. PTU is preferred in thyroid storm, pregnancy, and lactation. Selection of the correct initial antithyroid drug dose requires clinical experience and judgment in order to strike a balance between the drug’s risk of side effects and its ability to normalize thyroid function. Controlled trials have shown that the optimal duration of antithyroid therapy is about 12 to 18 months.

REFERENCES


