# Long-term antithyroid drug therapy

*David S. Cooper*

**Purpose of review**
Over the last 1–2 decades, patients and physicians have preferred antithyroid drug therapy as the initial treatment of Graves' disease, rather than radioactive iodine or surgery. More recently, the concept of long-term antithyroid drug therapy (LTADT; >24 months of treatment) has also become increasingly popular.

**Recent findings**
Data from cohort studies and a prospective randomized trial suggest that LTATD therapy is safe and is associated with a higher chance of remission from Graves' disease than is shorter-term therapy. Also, LTADT may be associated with better quality of life and other clinical outcomes compared to radioiodine and surgery.

**Summary**
Long-term antithyroid drug therapy is appropriate for children and young adults. This approach is a reasonable option in those who are doing well on a stable low dose of antithyroid drug therapy, and especially those who wish to avoid definitive treatment with radioactive iodine or surgery, given their inherent risks and need for lifelong hormonal replacement therapy.

**Keywords**
Graves' disease, hyperthyroidism, methimazole, remission, anti-thyrotropin receptor antibodies

## INTRODUCTION

The modern era of antithyroid drug therapy began in 1943 with the publication of the first clinical experience with thionamide therapy for Graves' disease [1], establishing a new, nondestructive model for treating hyperthyroidism. It was not long before it was noted that some patients treated with antithyroid drugs for one to two years had 'remissions', that is, remained euthyroid long after the medication had been discontinued [2]. Of course, the concept of spontaneous remission from Graves' disease had been noted by others long before that [3], but the notion that this could occur with higher frequency after antithyroid drug therapy was an exciting concept. Subsequently, it was noted that when patients experienced remissions, relapses typically occurred earlier (i.e., within the first year or two after drug cessation) rather than later [4]. Hershman *et al.* [4] found that of 176 patients followed for at least 6 years after antithyroid drugs were stopped, 54% experienced remissions that continued for 6–20 years; 70% of the recurrences occurred within the first year after treatment had been discontinued, and relapses after >6 years of follow-up were unusual (2.8%). Subsequently, the idea that antithyroid drugs could be restarted and used to treat relapsed patients for a protracted period of time, even for a lifetime, was proposed as an alternative to radioiodine therapy or surgery as far back as the 1960s and 1970s [5,6].

## TRENDS IN THERAPY FOR GRAVES' DISEASE

Despite the recommendations by some experts that antithyroid drug therapy could be used for long periods of time [5,6], by the 1980s, radioactive iodine therapy had become the dominant treatment option for therapy of hyperthyroidism in the United States [7], albeit not the rest of the world [8]. The prevailing thinking was that patients with more severe biochemical derangements, larger goiters, and higher serum levels of anti-TSH receptor antibodies (TRAb) were not good candidates for primary antithyroid drug therapy because of their perceived low chances of remission. This notion was

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**Curr Opin Endocrinol Diabetes Obes** 2021, 28:510–516
DOI:10.1097/MED.0000000000000656

## KEY POINTS

- Long-term antithyroid drug therapy of Graves' disease (therapy for >2 years) has been shown to be associated with an increase in remission rates compared to shorter durations of therapy.
- Long-term antithyroid drug therapy is relatively safe compared to radioiodine therapy and thyroidectomy.
- Patients should be informed about the option of long-term antithyroid drug therapy versus definitive therapy with radioiodine or surgery if, after 12–24 months of antithyroid drug therapy, there is persistent elevation of serum thyrotropin receptor antibodies titers.
- Long-term antithyroid drug therapy is appropriate for a large proportion of patients with Graves' disease including children, young adults, and older adults up to age 50 or 60 years whose thyroid function is stable on relatively low doses of methimazole (i.e., 2.5–10 mg per day).

substantiated by retrospective data that were used to predict the chances of remission based on clinical and laboratory parameters [9]. Therefore, primary antithyroid drug therapy was typically recommended as primary therapy largely for patients with a perceived higher likelihood of remission [10], such as those with only mild biochemical thyroid dysfunction, small goiters, and lower serum TRAb titers.

However, beginning in the early 2000s, there has been a reversal in the United States toward a preference for antithyroid drug therapy as primary treatment [11]. Insurance claims data show that antithyroid drugs are now the initial treatment for the majority of patients with Graves' disease [11], and many patients prefer to continue drug therapy for long periods of time, rather than receive definitive treatment with radioiodine or surgery [12▪]. The reasons for this dramatic change are multiple, and include patient dissatisfaction with the therapy of permanent hypothyroidism [13,14], radiation exposure, the controversy over the potential for subsequent malignancy [15▪], and the prospect of worsening or the new onset of thyroid eye disease after radioiodine [16]. Surgery remains a singularly unpopular primary treatment, likely due to its invasiveness and the possibility of relatively significant complications [11].

Despite these changes in patients' preferences for therapy, professional groups such as the American Thyroid Association [10] and the European Thyroid Association [17] have recommended that primary antithyroid drug therapy should last for 12–18 months, based on the results of randomized controlled trials done in the 1990s showing that remission rates were not influenced by the duration of primary antithyroid drug therapy, as long as the initial treatment was longer than 6 months [18–21]. If, after that time, serum TRAb titers remain persistently elevated, then the recommendations are that definitive therapy with radioiodine or surgery 'should be considered' [10,17]. However, 'continued low-dose methimazole treatment for longer than 12–18 months may be considered in patients not in remission who prefer this approach' [10].

One of the assumptions underlying a 12–18 month treatment period for antithyroid drugs, and then stopping therapy if serum TRAb levels become negative, is that most patients will have long-term remissions. However, the chance of relapse after this relatively brief period of therapy is considerable. For example, Carella *et al.* [22] found that approximately 20% of patients with normal serum TRAb levels relapsed over a median follow-up period of 15 months, with one patient relapsing as late as 10 years later. Laurberg *et al.* [23] similarly reported that approximately 30% of patients with negative serum TRAb levels after 18 months of antithyroid drug therapy relapsed over a follow-up period of 5 years, with some patients relapsing as late as five years after drug withdrawal. Most recently, Bandai *et al.* [24] reported on a cohort of 497 patients with Graves' disease and positive serum TRAb titers treated with antithyroid drugs (Fig. 1). After initiation of therapy, serum TRAb levels normalized in >75% of patients. The serum TRAb titers normalized after 2 years of therapy in 274 patients (49.9%), and after 2–5 years in 107 additional patients, for a total of 433 patients (79%), with a mean time to TRAb normalization of 1.5 years (±2 SD 0.3–8.1 years). After withdrawal of antithyroid drug therapy after an arbitrary 12–18 months, 52% of these patients had permanent resolution of TRAb positivity, with an overall remission rate of 89%. However, even when serum TRAb levels normalized, 48% of patients had a 'fluctuating' pattern of TRAb titers, with repeated increases followed by decreases after reinstitution of therapy over the ensuing 2–10 years, with a significantly lower remission rate of 38% [24]. The third group of patients ($n = 116$ or approximately 21% of the study group) had persistently positive serum TRAb levels for >5 years (or a 'smoldering course'), but even in this group, approximately 20% of patients had gradual decreases of TRAb levels over time and achieved remission after > 5 years of therapy.

## LONG-TERM ANTITHYROID DRUG THERAPY

The trend toward using antithyroid drugs as the primary treatment of Graves' disease has led to a

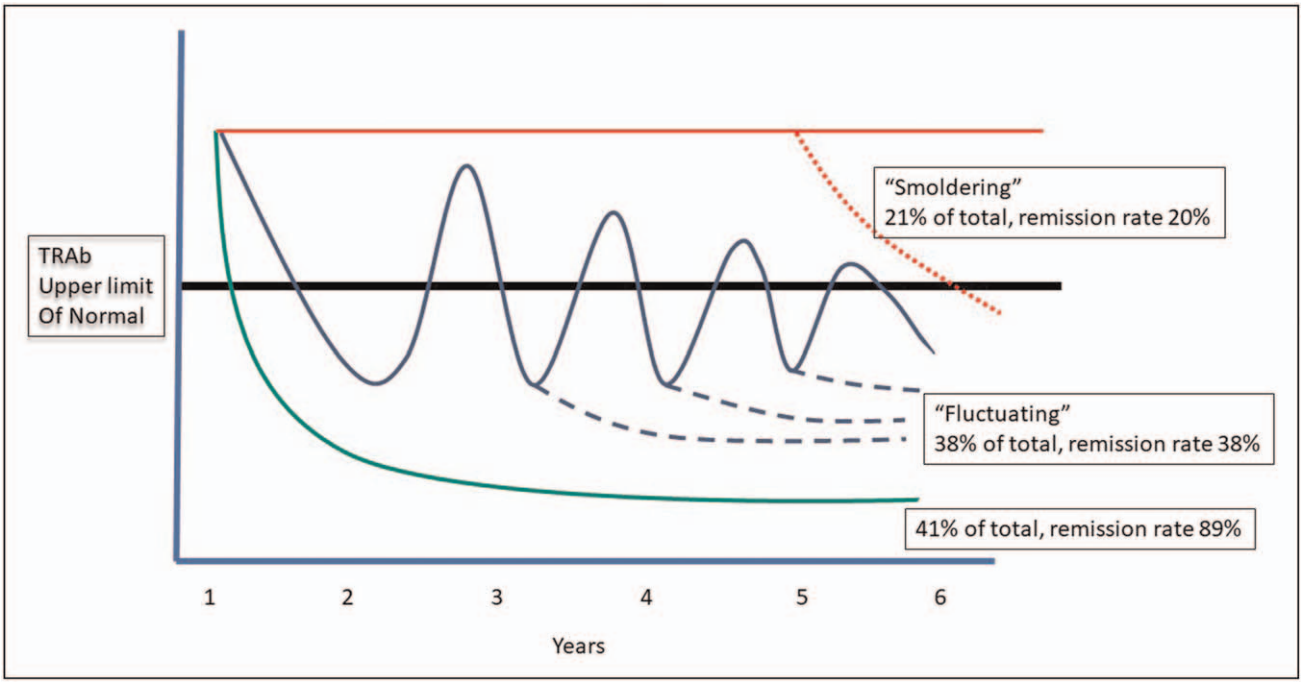


**FIGURE 1.** adapted from data in [24] and from [51]. Group A: 41% of patients had early and long-lasting TRAb normalization and a remission rate of 89%. Group B: 38% had a fluctuating course, with TRAb levels normalizing and then rising again, leading to relapse, with an overall remission rate of 37%. Group C: 21% had a smoldering course with TRAb levels that were persistent, but some (20%) had remissions after >5 years of methimazole therapy. TRAb, thyrotropin receptor antibodies.

renewed interest in prolonged antithyroid drug therapy, regardless of the perceived chances of remission, an approach that had been promoted decades earlier, as noted above [4–6]. Generally speaking, long-term drug therapy (LTATD) refers to therapy lasting longer than 24 months [25]. The willingness to re-examine the utility of LTATD therapy, despite the data from the earlier randomized trials showing that treatment duration did not influence relapse rates [18–21], is based on newer data that have become available from cohort studies published in the last decade, demonstrating that longer-term antithyroid drug therapy (up to 8 years) led to higher remission rates compared to shorter durations of therapy [26–28]. For example, Liu *et al.* [28] studied 128 patients with recurrent hyperthyroidism after 12 months of methimazole therapy. Patients were restarted on methimazole, and when the drug dose was decreased to 2.5 mg a day, patients were randomized to short-term methimazole therapy (median 15 months, [duration range 5–51 months]) versus longer-term therapy (median 20 months [duration range 9–93 months]). The patients were followed for 48 months after drug withdrawal, with remission rates of 67% in the group receiving 'short-term' methimazole versus an 85% remission in the longer-term group [$P = 0.02$]. In a retrospective study of 135 patients treated with antithyroid drug therapy, 82 (61%) remained in remission after drug withdrawal after a median of 39 months of therapy [29]. The likelihood of remission was associated with the absence of eye disease, milder biochemical dysfunction at baseline, female sex, nonsmoking status, and duration of thionamide therapy >24 months. In multivariate analysis, drug therapy for >24 months was the only independent predictor of the duration of remission. A meta-analysis by Azizi *et al.* [30] of six studies of long-term antithyroid drug therapy (treatment duration of 41–98 months in six studies), showed that there was a positive relationship between odds of remission and duration of therapy, with a calculated 16% greater chance of remission for every year of antithyroid drug treatment.

Most recently, Azizi *et al.* [31] conducted a randomized trial comparing a conventional course of antithyroid drug therapy to a longer duration of treatment. These investigators treated 258 patients with Graves' disease with methimazole for 18–24 months. They were then randomized to discontinue methimazole or continue methimazole for an additional 36–102 months (total treatment duration 60–120 months). Methimazole was then stopped and patients were followed for 48 months. Relapse rates were 53% in the group taking 'short-term' methimazole compared to 15% in those

patients receiving 'long-term' therapy ($P < 0.001$). Approximately 8% of the 'long term' group developed transient subclinical hyperthyroidism that was not treated, because all patients were <65 years of age. A minority of patients (<10%) ultimately developed permanent hypothyroidism on long-term follow up. A subsequent cohort study by Azizi *et al.* [32] reported on a group of 59 patients with Graves' disease treated with methimazole for 14 years. Thirty-two patients then discontinued methimazole, and 27 preferred to remain on methimazole indefinitely. All patients were followed for a mean of six additional years. In the 32 patients who stopped methimazole, relapse occurred in 6 (19%), whereas of the 27 patients who continued methimazole for up to the total of 24 years all remained euthyroid and with negative serum TRAb titers. The mean dose of methimazole to maintain normal thyroid function decreased gradually over time and was approximately 2.5 mg/day after 24 years of treatment. No adverse reactions to methimazole occurred over 24 years of therapy in any of the patients.

The safety of LTADT was also reported in a literature review by Azizi *et al.* [33], confirming that serious adverse events such as agranulocytosis and hepatotoxicity occur almost inevitably in the first 3–6 months of therapy [34], and rarely occur after 12–18 months, the time when long-term antithyroid drug therapy actually begins. In this review of 12 papers incorporating 1660 pediatric and adult patients treated with antithyroid drugs for a mean treatment duration of 5.8 years, there were only five adverse reactions that occurred after 1 year of treatment [33], including a patient with vasculitis after 6 years of treatment with propylthiouracil [27], and, in two cohorts of children treated with methimazole [35,36], a rash occurred after five years of treatment in one patient, neutropenia occurred after 3, 9 and 11.5 years of treatment in three patients [35,36], and arthralgias occurred after 7 years in one patient [36].

A major potential advantage of LTATD, compared to destructive treatment with radioiodine and surgery, includes the fact that patients do not require lifelong thyroid hormone replacement therapy to treat postablative hypothyroidism. As noted above, treated hypothyroidism has been shown in some studies to be associated with a significant degree of persistent symptoms suggestive of hypothyroidism, as well as patient dissatisfaction [13,14]. However, differences in quality of life [QoL] and other standardized measures of patient well being have been difficult to demonstrate. For example, a 14–20-year follow-up study of Graves' disease patients previously enrolled in a prospective trial in which they had been randomized to be treated with antithyroid drugs, radioiodine, or surgery, found that overall QoL measures (using the Medical Outcome Study 36-item Short Form Health Status Survey [SF-36]), were similar to the general Swedish population. However, there were significantly lower QoL scores in the mental health domain of 'vitality' for all Graves' disease patients, regardless of their prior therapy [37]. Similarly, another long-term follow-up study from Scandinavia [38] of a cohort of 1176 patients with Graves' disease treated with all three modalities 6–10 years previously showed worse scores on a thyroid-specific Thyroid-related Patient Reported Outcome Questionnaire (ThyPRO) in all patients compared to the general population. However, the patients who had been treated with radioiodine had worse thyroid related and general QoL scores, which persisted after adjustment for age, compared to patients who had been treated with antithyroid drugs or surgery [38].

In a randomized study by Azizi *et al.* [39], patients with recurrent hyperthyroidism after a course of antithyroid drugs were assigned to receive radioiodine therapy ($N = 51$) or low dose methimazole ($N = 34$). Over a follow-up period of approximately 10 years, patients treated with radioactive iodine more often had both elevated and low serum thyrotropin (TSH) levels (relative risk [RR] = 2.2 [95% confidence interval (CI) 1.53–3.09, $P < 0.01$]) and dyslipidemia. Not unexpectedly, patients treated with radioiodine had a goiter less frequently [39]. QoL scores using the SF-36 were similar between the two groups. More recently, Villagelin *et al.* [40] conducted a retrospective study of 238 patients treated with methimazole for 12–18 months who had suffered a relapse. There were 124 patients who chose to receive radioactive iodine, while 114 patients resumed chronic methimazole therapy. After a mean follow-up period of >5 years, more patients who had received radioactive iodine therapy had elevated serum TSH levels, indicating inadequate thyroid hormone replacement therapy and/or disease monitoring. Furthermore, patients who had received radioactive iodine had gained significantly more weight, and they also were more likely to experience worsening of thyroid eye disease [40]. However, similar to the report by Azizi *et al.* [39], there were no differences in QoL scores between the two groups.

## POTENTIAL MECHANISMS OF ANTITHYROID DRUGS TO AMELIORATE THYROID AUTOIMMUNITY

If antithyroid drug therapy is related to remission rates, what would the mechanism possibly be? Some have suggested that untreated hyperthyroidism perpetuates a dysregulated immune system, and that

restoration of normal thyroid function then allows recovery from the aberrant autoimmune attack [41,42]. A second possibility is that antithyroid agents have direct effects on the immune system, causing a decrease in the autoimmune diathesis. Clearly, the observed decreases in serum TRAb levels and increases in suppressor T cells with antithyroid drug therapy [43] could be due to either indirect direct effects, or both. However, there are in in-vivo and in-vitro studies suggesting that thionamide antithyroid agents can have direct effects on the immune system, including inhibition of antithyroid antibody production by lymphocytes [44], and effects on human leukocyte antigen-DR expression by thyrocytes, impairing their ability to serve as antigen presenting cells [45,46]. As of now, there has not been a resolution to the question of whether indirect or direct effects on the immune system predominate in the ultimate achievement of remissions in patients with Graves' disease.

## SELECTION OF PATIENTS FOR LONG-TERM ANTITHYROID DRUG THERAPY

If the strategy of LTATD were to be initiated, which patients would be the most likely to benefit? In my view, patients on stable doses of an antithyroid drug with a history of relapses would be excellent candidates. Children and young adults who are concerned about the potential long-term effects of radioiodine and/or wish to avoid surgery would also be appropriate. Indeed, the ETA recommends a 36-month initial treatment period for children with Graves'' disease [17]. Patients with thyroid eye

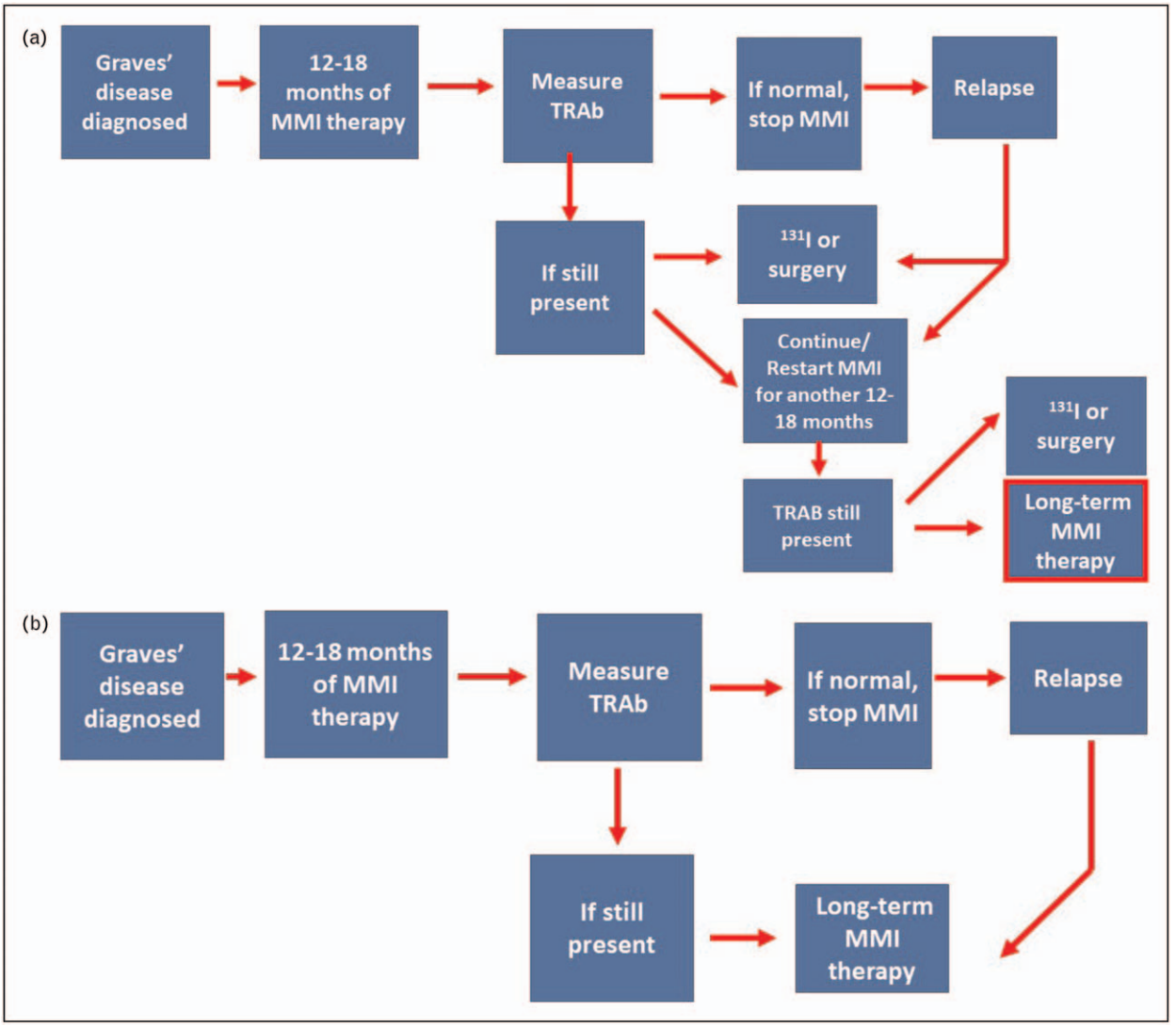


**FIGURE 2.** Algorithms for the management of Graves' disease. (a) Management strategy as recommended by current clinical practice guidelines [10,17]. (b) Implementation of long-term antithyroid drug therapy.

disease who are concerned about its worsening after radioiodine therapy would also be good candidates. Finally, any patient with Graves' disease who wishes to avoid ablative therapy and who is doing well on a stable dose of methimazole should be considered. On the other hand, one might argue that older persons with Graves' disease (e.g., those over age 60 or 65 years) might have better outcomes if they are treated definitively with radioiodine, or less often surgery, because of concerns related to the potential deleterious cardiovascular [47,48] and skeletal effects [49] of recurrent or persistent hyperthyroidism in the older population.

## IMPLEMENTATION OF LONG-TERM ANTITHYROID DRUG THERAPY

Long-term antithyroid drug therapy has a different management algorithm than has been traditionally utilized in the management of Graves' disease with antithyroid drugs (Fig. 2a). As noted earlier, the current strategy is to treat patients for 12–18 months with antithyroid drugs, and, if serum TRAb levels are not below a specific cutoff, then patients should seriously consider definitive therapy with radioiodine or surgery [10,17]. While continuation of antithyroid drug therapy for an additional 12–18 months is also an option in patients wishing to avoid ablative treatment, this strategy seems to be favored more by European [17] compared to American experts [10]. But, if serum TRAb levels remain persistently elevated after an additional 12 months of therapy, definitive treatment is recommended [17]. In contrast, the concept of LTATD therapy means that patients will be maintained on drug therapy until serum TRAb levels normalize, or indefinitely if they persist (Fig. 2b). In patients whose serum TRAb levels normalize but who then suffer a recurrence, drug therapy would be reinstituted for an indefinite period of time. It should be recalled that agranulocytosis can occur in patients who had a prior uneventful exposure to a drug when restarting it, typically when the interval between courses of therapy has been >6 months [50]. The data of Azizi *et al.* [31] strongly suggest that a 5–10 years treatment period leads to remissions in >80% of patients who are followed for 48 months. Serum thyroid function testing every 4–6 months, annual follow-up visits, and measurement of serum TRAb titers seem like reasonable follow-up management, but there is no standardized method of monitoring patients on LTADT. Some have suggested that LTADT for Graves' disease is similar to treating other chronic illnesses with safe and effective medications [32], such as hypertension, dyslipidemia, and diabetes.

## CONCLUSION

Long-term antithyroid drug therapy should be considered a viable option for patients with Graves' disease whose hyperthyroidism is well controlled on a stable dose of medication, and who prefer this form of therapy over radioiodine or surgery. Ongoing monitoring of thyroid function is essential, as is continued patient input about continuing medical therapy. In women of childbearing age who desire pregnancy, ongoing methimazole therapy needs to be reconsidered, and alternative strategies, such as stopping methimazole if the serum TRAb titer is negative, or, if the TRAb is still positive, switching to propylthiouracil (PTU), or accepting radioiodine or surgical treatment. Ideally, LTADT should be compared to definitive treatment with radioiodine and surgery in a large prospective randomized controlled trial with adequate numbers of patients and long-term follow-up, including data on differences in cost-effectiveness and QoL measures.

### Acknowledgements

*None.*

### Financial support and sponsorship

*None.*

### Conflicts of interest

*There are no conflicts of interest.*

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- ■ of special interest
- ■■ of outstanding interest

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