A systematic review of drug therapy for Graves’ hyperthyroidism

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Abstract
We assessed the effects of dose, regimen and duration of anti-thyroid drug therapy for Graves’ thyrotoxicosis on recurrence of hyperthyroidism, course of ophthalmopathy, adverse effects, health-related quality of life and economic outcomes. We undertook a systematic review and meta-analyses of randomised controlled trials (RCTs). We identified RCTs regardless of language or publication status by searching six databases, and trial registries. Dual, blinded data abstraction and quality assessment were undertaken. Trials included provided therapy for at least 6 months with follow-up at least 1 year after drug cessation. Fixed or random effects meta-analyses were used to combine study data. Twelve trials compared a Block-Replace regimen (requiring a higher dose of anti-thyroid drug treatment) with a Titration regimen. Overall, there was no significant difference between the regimens for relapse of hyperthyroidism (relative risk (RR) = 0.93, 95% confidence interval (CI) 0.84 to 1.03). Participants were more likely to withdraw due to adverse events with a Block-Replace regimen (RR = 1.89, 95% CI 1.25 to 2.85). Prescribing replacement thyroxine, either with the anti-thyroid drug treatment, or after this was completed, had no significant effect on relapse. Limited evidence suggested 12–18 months of anti-thyroid drug treatment should be used. The titration regimen appeared as effective as the Block-Replace regimen, and was associated with fewer adverse effects. However, relapse rates over 50% and high participant drop-out rates in trials mean that the results should be interpreted with caution, and may suggest that other strategies for the management of Graves’ disease, such as radioiodine, should be considered more frequently as first-line therapy. There were no data on the course of ophthalmopathy, health-related quality of life and economic outcomes.

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Introduction
Hyperthyroidism is common, affecting approximately 2% of women and 0.2% of men (1). The most common cause of hyperthyroidism is Graves’ disease (1). Methimazole, carbimazole and propylthiouracil are the main drug treatments, blocking thyroid hormone synthesis. They may also help control thyrotoxicosis by immune suppression. Propylthiouracil additionally inhibits the peripheral conversion of thyroxine (T4) to triiodothyronine. Methimazole is the active metabolite of carbimazole, and since the conversion of carbimazole to methimazole is virtually complete, equivalent doses are thought to be comparable. Anti-thyroid drug therapy can be given either by the Block-Replace regimen (where a higher dose of anti-thyroid drug is used with a replacement dose of thyroid hormone) or by the Titration regimen (where the anti-thyroid drug dose is reduced by titrating treatment against thyroid hormone concentrations).

The preferred regimen and duration of therapy remain unresolved with varying duration from 6 to 24 months with either the Block-Replace or the Titration regimen. We undertook a substantial update to a Cochrane systematic review (2) assessing the effects of anti-thyroid drug regimen and duration in the treatment of Graves’ hyperthyroidism.

Methods
PA was involved in protocol development, searching for trials, quality assessment of trials, data abstraction and data analysis. A A was involved in protocol development, quality assessment of trials, data abstraction and data analysis. W A W was involved in searching for trials, quality assessment of trials and data abstraction. C M P undertook quality assessment of trials and data abstraction. J S B provided clinical input, and resolution of differences of opinion. No Ethics approval was required.
**Search strategy for identification of studies**

We identified relevant studies regardless of language or publication status by searching The Cochrane Central Register of Controlled Trials (CENTRAL) (Issue 1, 2004), MEDLINE (1966 to July 2004), EMBASE (1980 to July 2004), BIOSIS (1985 to July 2004), CINAHL (1982 to July 2004), HEALTHSTAR (1975 to June 2002) and trial registries. We contacted authors of published trials and thyroid researchers and checked the references of retrieved studies and reviews for additional trials. Three trialists provided additional data.

**Selection**

We included all published and unpublished, randomised and quasi-randomised controlled trials (RCTs) of patients of any age receiving anti-thyroid drug treatment for Graves’ hyperthyroidism, where Graves’ hyperthyroidism had been adequately defined. We pre-specified a minimum duration for drug treatment of 6 months and a minimum duration of follow-up of 1 year from completion of drug therapy to assess the pre-specified outcomes.

We sought trials of carbimazole, propylthiouracil, methimazole, lithium or perchlorate. We pre-specified the comparisons of Block-Replace vs Titration regimen; short-term (6 months) vs long-term (over 6 months) regimens; high-dose drug therapy (equivalent to 40 mg carbimazole or more) vs low-dose (equivalent to 30 mg carbimazole or less); and continued thyroid hormone replacement with or without continued anti-thyroid medication.

The main outcome measures were recurrence of hyperthyroidism, incidence of hypothyroidism and mortality. Additional outcome measures sought were the course of ophthalmopathy (need for corticosteroids, radiotherapy, visual compromise); adverse effects (agranulocytosis, drug rash, hepatitis, vasculitis); symptoms of hyperthyroidism (anxiety, tachycardia, heat intolerance, diarrhoea, oligomenorrhoea); thyroid antibody status; weight change; frequency of outpatient visits and thyroid function tests; health-related quality of life; economic outcomes; compliance; and necessity for surgery or radioiodine.

**Validity assessment**

Quality assessment of RCTs included allocation concealment, whether intention-to-treat analysis was undertaken, comparability of groups at baseline, and blinding of outcome assessors. The summary risk of bias was based on the concealment of allocation.

**Data abstraction**

Two reviewers independently abstracted the data and assessed the methodological quality of the studies.

Any differences were resolved by discussion between the reviewers.

**Quantitative data synthesis**

Where appropriate, the results of comparable groups of trials were combined for relative risks (RRs) using fixed-effects models, and results are presented with 95% confidence intervals (CIs). Heterogeneity between comparable trials was assessed by the I² statistic (3). Random effects models were used where I² was 50% or more. Pre-specified subgroup and sensitivity analyses were undertaken.

**Results**

**Trial flow**

Twenty-three RCTs were included in the review (Fig. 1). All studies included adults only. Overall 83% of participants were women, and the weighted mean age was 40 years.
Duration of anti-thyroid therapy (Table 1, Fig. 2)

In one study (4, 5) the longer-duration Titration regimen (18 months) had significantly fewer relapses than the 6 month group (RR = 0.63, 95% CI 0.41 to 0.99). One study (6) found there was no significant difference between 12 and 6 months (RR = 0.86, 95% CI 0.52 to 1.43) using the Block-Replace regimen.

Two other studies used longer durations of Titration regimen, comparing 12 months with 24 months (7) and 18 months with 42 months of therapy (8). Combining these showed no significant difference between the longer and shorter durations of treatment (RR = 0.88, 95% CI 0.67 to 1.16).

Block-Replace vs Titration regimen (Table 2, Figs 3 and 4)

The anti-thyroid drug used was carbimazole in eight studies (9–16). The dose ranged between 30 and 60 mg/day in the Block-Replace arms of all these studies except for one study (11), where a dose of 100 mg/day was used. Methimazole was used in three studies (17–20) where doses of 30–60 mg/day were used in the Block-Replace arms of the trials. One study (21) used either propylthiouracil or methimazole but the doses were not reported. The duration of therapy was 6 months in two studies (11, 19), 18 months in four studies (9, 10, 15, 20) and 12 months in the remaining trials (duration of therapy in one study (21) is unknown).

Including all trials, irrespectively of length of follow-up, there was no significant difference in the relapse rates between the Block-Replace (322 of 636; 51%) and Titration (332 of 614; 54%) regimens (RR = 0.93, 95% CI 0.84 to 1.03) when the losses to follow-up were not considered. However, there were large losses to follow-up, with 234 and 223 in the Block-Replace and Titration groups respectively. Excluding one study (17, 18) with a loss to follow-up of 44% had no major effect on the overall results (RR = 0.91, 95% CI 0.81 to 1.03). When analysis was carried out making the extreme assumption of relapsed hyperthyroidism in participants lost to follow-up there was a significant difference between the two groups, with relapse rates of 63% (549 of 870) in the Block-Replace group and 68% (566 of 837) in the Titration group (RR = 0.93, 95% CI 0.87 to 0.99). Therefore the true relapse rates with either of these anti-thyroid drug regimens would be between 51 and 68%.

Data regarding side-effects and number of participants withdrawn from therapy due to side-effects were available in seven studies (11, 13, 14, 16–19). The number of participants reporting rashes was significantly higher in the Block-Replace trial arms.
(10%, 63 of 616) as compared with the Titration arms (5%, 31 of 622) (RR = 2.04, 95% CI 1.36 to 3.06).

The Block-Replace regimens also had more patients with agranulocytosis compared with the titration group (nine vs three). There was one further report of agranulocytosis in one study (20) but the treatment group was not mentioned. The number of participants withdrawing due to side-effects was also significantly higher on the Block-Replace regimen (RR = 1.89, 95% CI 1.25 to 2.85). The study (11) using the highest dose of 100 mg carbimazole had 7 of 17 patients in the Block-Replace regimen withdrawing due to side-effects including two cases of agranulocytosis and five with rashes, compared with one case of agranulocytosis from participants on the Titration regimen.

**Initial and continued low-dose anti-thyroid drug therapy compared with no additional T4 (Table 3, Fig. 5)**

Combining the data from three studies (22–24) adding in T4 led to fewer relapses (RR = 0.65, 95% CI 0.14 to 3.00, random effects model). There was marked heterogeneity (I² = 88%) with the result being largely influenced by one study (22) where the relapses in the T4 group were less than 2% compared with 35% in the placebo group. A sensitivity analysis with the exclusion of this study also yielded no significant difference in the relapse rates.

**Initial anti-thyroid drug therapy followed by T4 compared with no T4 (Table 3, Fig. 5)**

Three studies (25–29) gave anti-thyroid drugs for 12–18 months and then randomised into groups receiving either T4 or no treatment. One study (25, 26) randomised the T4 group further at the end of the first year into groups either stopping or continuing T4 (only the results of the initial randomisation with results at the end of the first year were considered in the analysis). One study (13) had a factorial randomisation such that following a period of anti-thyroid drugs (Block-Replace compared with Titration) one group continued T4 for 1 year and the second group had no therapy after anti-thyroid medications. On combining the results of these four studies for T4 there was no statistically significant difference in the relapse rates between the two groups after 12 months of follow-up (RR = 1.09, 95% CI 0.86 to 1.39).

**Drug choice**

Among the studies that reported rashes, 7% (19 of 264) participants on carbimazole developed rashes, and 12% (82 of 714) of participants on methimazole.
Five cases of agranulocytosis occurred in participants on methimazole and four cases in participants on carbimazole (two participants were taking very high doses of 100 mg carbimazole/day).

Other outcomes

None of the trials reported the effects of the different treatment regimens on progress of ophthalmopathy, quality of life, use of healthcare resources, or undertook an economic evaluation.

Discussion

The optimal medical therapy for Graves’ hyperthyroidism remains a subject of debate. There are several choices to be made when considering the drug treatment of Graves’ hyperthyroidism: which drug, dose...
and duration of therapy, whether to add T4, and when to discontinue therapy. This review examines the evidence from the RCTs conducted in this field. The results need to be interpreted with some caution as several of the trials had large losses to follow-up. In the Block-Replace vs Titration regimens, there was a total loss to follow-up of 27%. The reasons for the large loss to follow-up are unclear and may include: patients feeling relatively well a few weeks after commencement of therapy and attainment of euthyroidism; relatively younger age group of patients likely to have work and other commitments such that once euthyroidism is attained, they fail to comply with therapy and have a variable lag period before a relapse occurs; other motives leading to poor compliance with therapy including maintenance of weight loss in young to middle aged women; and different health systems in different countries with varying follow-up mechanisms.

With regard to the duration of therapy, there is some evidence that 12-18 months of drug therapy is more effective than shorter durations. This is stronger with use of the Titration regimen (4, 5) than for the Block-Replace regimen (6), although the latter study was a quasi-randomised study. Two of the studies (7, 8) using longer durations of therapy did not show any clear evidence of benefit in extending therapy beyond 18 months, although the CIs were wide.

Longer-term follow-up data (2–5 years after completion of anti-thyroid drug therapy) showed no evidence to suggest that the Block-Replace therapy reduces relapse rates when compared with the standard Titration regimen. None of the studies examined differences in the rates of ophthalmopathy progression or looked at any quality of life indicators. There was in fact a significantly higher rate of drug withdrawal due to side-effects (16 vs 9%), a significantly higher incidence of rashes (10 vs 5%) and more episodes of agranulocytosis (nine vs three) in the Block-Replace group. The use of higher doses (carbimazole 100 mg daily) in one study (11) led to unacceptably high rates of side-effects, including a 12% (2 of 17) incidence of agranulocytosis, a potentially life-threatening complication. Seven of the 17 (46%) participants withdrew from the Block-Replace group due to the side-effects (11). The increased side-effects of the higher drug doses required for the Block-Replace regimen and the lack of evidence in the longer term about its effectiveness over the Titration regimen would prejudice choice in favour of the Titration regimen. Some of the reasons that the Block-Replace regimen is preferred include the better maintenance of the euthyroid state and concerns regarding the effects of transient periods of hypothyroidism on quality of life and in Graves’ ophthalmopathy where hypothyroidism may be detrimental to the progression of the eye disease. Unfortunately none of the RCTs looked at this issue and there is

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<tr>
<th>Trial</th>
<th>Location</th>
<th>Intervention</th>
<th>Duration of therapy</th>
<th>Duration of follow-up (mean)</th>
<th>Patients randomised/assessed at close of study</th>
<th>Relapse rates (% (numbers))</th>
<th>Methodological rating for concealment of allocation</th>
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<tr>
<td>Combined ATD and T4</td>
<td>Japan</td>
<td>MMI for 6 months then 1: MMI 10 mg + T4 2: MMI 10 mg + placebo alone for 3 years</td>
<td>12 months (then T4 or placebo alone for 3 years)</td>
<td>3 years</td>
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<td>Pfeilschifter &amp; Zeigler</td>
<td>Germany</td>
<td>CBZ till euthyroid then 1: CBZ 10 mg + T4 to keep TSH &lt; 0.03 mU/l 2: CBZ 10 mg and T4 if TSH &gt; 4 mU/l</td>
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<td>12 months</td>
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<td>12–31 months</td>
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<td>Continued T4 alone</td>
<td>Belgium multicentre</td>
<td>MMI 150–30 mg (or PTU) with T4 as needed for euthyroidism for 15 months then 1: T4 100 μg 2: Placebo ATD for 12–15 months, euthyroid off ATD for 1 month then 1: T4 to keep TSH &lt; 0.3 2: No treatment</td>
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<td>Nedrebo et al. (2002)</td>
<td>Norway multicentre</td>
<td>CBZ titrated (or CBZ 40 mg + T4) for 12 months then 1: T4 alone 2: No treatment</td>
<td>12 months</td>
<td>13.4–41.7 months</td>
<td>1: 108/93 2: 110/96</td>
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Abbreviations: CBZ: carbimazole; MMI: methimazole; PTU: propylthiouracil; T4: levothyroxine; T3: liothyronine; ATD: antithyroid drugs; TSH: thyrotropin-stimulating hormone; NS: not stated. Methodological rating for concealment of allocation: A, method did not allow disclosure of assignment; B, small, but possible chance of disclosure of assignment, or states ‘random’ but no description; C, quasi-randomised (alternate allocation to groups).
There is no clear evidence in favour of giving thyroid hormone supplementation following the initial treatment of Graves' thyrotoxicosis with anti-thyroid medication. The discrepant result from one study (22) could be due to higher iodine intake in Japan and/or differences in immunological or genetic factors (30). The trials which have subsequently tried to reproduce this study have all used differing protocols and none has used the original protocol used by Hashizume et al. (22).

The relapse rates obtained in our review were 51% for the Block-Replace regimen and 54% for the Titration regimen. The relapse rates were 63 and 68% for the Block-Replace and Titration regimens respectively when intention-to-treat analysis was carried out making the extreme assumption of relapsed hyperthyroidism in all drop-outs. It can be presumed that the true relapse rate for the anti-thyroid drug regimens is in the range of 51–68%. It could be argued that with such relapse rates, radioiodine therapy should be considered at an earlier stage in the UK, as appears to be the trend among American thyroidologists (31). It is possible that patients may also choose this modality of treatment, creating a stable situation earlier in the course of therapy and saving several years of regular outpatient clinic visits and possible upsets caused by relapses of hyperthyroidism. The possibility of long-term low-dose continuous anti-thyroid use has also been suggested in a recent trial with over 10 years of follow-up for 26 patients on low-dose methimazole (32).

**Evidence-based recommendations**

- The Titration regimen is just as effective as the Block-Replace regimen and, with a significantly lower incidence of adverse effects, should be considered as the first-line regimen in most situations.
- The evidence suggests the optimal duration of anti-thyroid drug therapy for the Titration regimen is 12–18 months.
- There is no benefit from continued T4 replacement after a course of anti-thyroid treatment.
- Radioiodine treatment should be discussed at an early stage – patients may choose this option when they are made aware of the likelihood of relapse and the need for prolonged outpatient clinic attendance with anti-thyroid drug treatment.

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Adequately powered trials which will look at the benefits of Block-Replace and Titration regimens on the progression of ophthalmopathy and quality of life are needed.

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