Hyperthyroidism (primary)

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ABSTRACT

INTRODUCTION: Hyperthyroidism is characterised by high levels of serum thyroxine and triiodothyronine, and low levels of thyroid-stimulating hormone. The main causes of hyperthyroidism are Graves' disease, toxic multinodular goitre, and toxic adenoma. About 20 times more women than men have hyperthyroidism. METHODS AND OUTCOMES: We conducted a systematic review and aimed to answer the following clinical questions: What are the effects of drug treatments for primary hyperthyroidism? What are the effects of surgical treatments for primary hyperthyroidism? What are the effects of treatments for subclinical hyperthyroidism? We searched: Medline, Embase, The Cochrane Library and other important databases up to June 2007 (BMJ Clinical Evidence reviews are updated periodically, please check our website for the most up-to-date version of this review). We included harms alerts from relevant organisations such as the US Food and Drug Administration (FDA) and the UK Medicines and Healthcare products Regulatory Agency (MHRA). RESULTS: We found 14 systematic reviews, RCTs, or observational studies that met our inclusion criteria. We performed a GRADE evaluation of the quality of evidence for interventions. CONCLUSIONS: In this systematic review we present information relating to the effectiveness and safety of the following interventions: adding thyroxine to antithyroid drugs (carbimazole, propylthiouracil, and thiamazole), antithyroid drugs (carbimazole, propylthiouracil, and thiamazole), radioactive iodine, and thyroidectomy.

QUESTIONS

INTERVENTIONS

DRUG TREATMENTS FOR PRIMARY HYPERTHYROIDISM

Likely to be beneficial

Unlikely to be beneficial

SURGICAL TREATMENTS FOR PRIMARY HYPERTHYROIDISM

Likely to be beneficial

TREATMENTS FOR SUBCLINICAL HYPERTHYROIDISM

Likely to be beneficial

Footnote

*Based on consensus, as RCTs would be considered unethical.

Key points

- Hyperthyroidism is characterised by high levels of serum thyroxine and triiodothyronine, and low levels of thyroid-stimulating hormone.

  Thyrotoxicosis is the clinical effect of high levels of thyroid hormones, whether or not the thyroid gland is the primary source.

  The main causes of hyperthyroidism are Graves' disease, toxic multinodular goitre, and toxic adenoma.

  About 20 times more women than men have hyperthyroidism.

- There is consensus that antithyroid drugs (carbimazole, propylthiouracil, and thiamazole) are effective in treating hyperthyroidism, although we found no evidence comparing them with placebo or with each other.

  We found no evidence that antithyroid drugs plus thyroxine (block-replace regimens) improved relapse rates compared with titration regimens.

  Higher-dose antithyroid drugs work better when taken for longer (more than 18 months) than for a shorter time (6 months).

  The doses of antithyroid drugs reported in the studies we found are higher than are generally used in practice.

- There is also consensus that radioactive iodine (radioiodine) is effective for hyperthyroidism.

  We don't know whether radioactive iodine increases risk of thyroid and extrathyroid cancer.

  Radioactive iodine can worsen ophthalmopathy in people with Graves' disease.

Giving antithyroid drugs to people having radioiodine may increase the proportion of people with persistent or recurrent hyperthyroidism or who need further treatment.

- There is consensus that thyroidectomy is effective for hyperthyroidism.

  Total thyroidectomy is more effective than subtotal thyroidectomy for hyperthyroidism.

  Replacement thyroxine will need to be given to people who become hypothyroid after thyroidectomy.

- There may be some improvement in bone mineral density and thyroid-stimulating hormone levels after treatment with antithyroid treatment in women who have subclinical hyperthyroidism.

DEFINITION

Hyperthyroidism is characterised by high levels of serum thyroxine (T4), high levels of serum triiodothyronine (T3), or both, and low levels of thyroid-stimulating hormone (TSH, also known as thyrotropin). Subclinical hyperthyroidism is characterised by decreased levels of TSH (less than 0.1 mU/L) but with levels of T4 and T3 within the normal range (total T4: 60–140 nmol/L; total T3: 1.0–2.5 nmol/L, depending on assay type). [1] The terms hyperthyroidism and thyrotoxicosis are often used synonymously; however, they refer to slightly different conditions. Hyperthyroidism refers to overactivity of the thyroid gland leading to excessive production of thyroid hormones. Thyrotoxicosis refers to the clinical effects of unbound thyroid hormones, whether or not the thyroid gland is the primary source. [2] Secondary hyperthyroidism due to pituitary adenomas, thyroiditis, iodine-induced hyperthyroiditis, and treatment of children and pregnant or lactating women are not covered in this review. Hyperthyroidism can be caused by Graves' disease (diffusely enlarged thyroid gland on palpation, ophthalmopathy, and dermopathy), toxic multinodular goitre (thyrotoxicosis and increased radioiodine uptake with multinodular goitre on palpation), or toxic adenoma (benign hyperfunctioning thyroid neoplasm presenting as a solitary thyroid nodule). [1] We have not included treatment of Graves' ophthalmopathy in this review, although we do report on worsening of Graves' ophthalmopathy with radioiodine. We have also not included euthyroid sick syndrome (a condition seen in people with, for example, pneumonia, MI, cancer, and depression — it is characterised by low levels of TSH and T3). **Diagnosis:** The diagnosis of hyperthyroidism is established by a raised serum total or free T4 or T3 hormone levels, reduced TSH level, and high radioiodine uptake in the thyroid gland along with features of thyrotoxicosis. The usual symptoms are irritability, heat intolerance and excessive sweating, palpitations, weight loss with increased appetite, increased bowel frequency, and oligomenorrhoea. People with hyperthyroidism also often have tachycardia, fine tremors, warm and moist skin, muscle weakness, and eyelid retraction or lag. [1]

INCIDENCE/ PREVALENCE

Hyperthyroidism is more common in women than in men. One study (2779 people in the UK, median age 58 years, 20 years' follow-up) found an incidence of clinical hyperthyroidism of 0.8/1000 women a year (95% CI 0.5/1000 women/year to 1.4/1000 women/year). [3] The study reported that the incidence was negligible in men. The incidence of hyperthyroidism is higher in areas of low iodine intake than in areas with high iodine intake, because suboptimal iodine intake induces nodular goitre, and by time the nodules become autonomic, hyperthyroidism develops. [4] In Denmark, an area characterised by moderate iodine insufficiency, the overall incidence of hyperthyroidism (defined as low levels of TSH) is 9.7%, compared with 1.0% in Iceland, an area of high iodine intake. The prevalence in this Danish study was 38.7/100,000 a year in women and 2/100,000 a year in men. [5]

AETIOLOGY/ RISK FACTORS

Smoking is a risk factor, with an increased risk of both Graves' disease (OR 2.5, 95% CI 1.8 to 3.5) and toxic nodular goitre (OR 1.7, 95% CI 1.1 to 2.5). [6] In areas with high iodine intake, Graves' disease is the major cause, whereas, in areas of low iodine intake, the major cause is nodular goitre. [5] A correlation between diabetes mellitus and thyroid dysfunction has been described. In a Scottish population with diabetes, the overall prevalence of thyroid disease was found to be 13%, highest in women with type 1 diabetes (31%). As a result of screening, new thyroid disease was diagnosed in 7% of people with diabetes (hyperthyroidism in 1%). [7]

PROGNOSIS

Clinical hyperthyroidism can be complicated by severe cardiovascular or neuropsychiatry manifestations requiring admission to hospital or urgent treatment. **Mortality:** One population-based 10-year cohort study of 1191 people aged 60 years and over found a higher mortality among people who had a low initial TSH level. The excess in mortality was attributable to CVD. However, the people in this study who had low TSH level may have had a higher prevalence of other illnesses, and adjustment was done only for age and sex, not for co-morbidity. [8] We found another population-based study evaluating 3888 people with hyperthyroidism. No increase was found in all-cause mortality or serious vascular events in people whose hyperthyroidism was treated and stabilised, but an increased risk of dysrhythmias was found in people treated for hyperthyroidism compared with standard population (standardised incidence ratio 2.71, 95% CI 1.63 to 4.24). [9] **Atrial fibrillation in people with overt hyperthyroidism:** We found one cohort study evaluating the incidence of atrial fibrillation in people aged over 60 years with low serum TSH concentrations (up to 0.1 mU/L). It found that low serum TSH concentrations were associated with an increased risk of atrial fibrillation

(diagnosed by ECG) at 10 years (61 people with low TSH, 1576 people with normal TSH; incidence of atrial fibrillation: 28/1000 person-years with low TSH values *v* 11/1000 person-years with normal TSH values; 13/61 [21%] with low TSH values *v* 133/1576 [8%] with normal TSH values; RR 2.53, 95% CI 1.52 to 4.20; RR calculated by *BMJ Clinical Evidence*). [10] A population-based study including 40,628 people diagnosed with hyperthyroidism in Denmark from 1977 to 1999 found that 8.3% were diagnosed with atrial fibrillation or flutter within ± 30 days from the date of diagnosis of hyperthyroidism. [11] **Quality of life:** Left untreated, thyroid problems can adversely effect quality of life in many ways, which can continue in the long term. In a long-term follow-up (179 people, treated for 14–21 years before investigation), people with Graves' disease, compared with a large Swedish reference population, had diminished vital and mental quality-of-life aspects even after years of treatment. [12] **Fracture rate and bone mineral density:** Hip and spine bone mineral density levels can decrease if hyperthyroidism is untreated. [13] However, when treated, bone mineral density can increase to normal levels. The risk of hip fracture is also higher in people with hyperthyroidism. Progression from subclinical to overt hyperthyroidism is seen in people with nodular goitre, but not in people found by screening to be without other signs of thyroid disease. [14] A meta-analysis (search date 1996) based on data from screening studies estimated that each year 1.5% of women and 1.0% of men who had a low TSH level and normal free T4 and T3 levels developed an elevated free T4 or free T3 level. [14] Ophthalmopathy is a complication of Graves' hyperthyroidism. Treatment can be problematic and usually involves topical corticosteroids and external radiation of the eye muscles. **Thyroid volume and the nodularity of the gland influence the cure rate of hyperthyroidism:** In a controlled study (124 people with newly diagnosed hyperthyroidism), remission rates were calculated after treatment with a combined antithyroid drug plus T4 for about 2 years. People with Graves' disease with no goitre or a small goitre had a significantly better outcome compared with people with Graves' disease with a medium-sized or large goitre. Most people with multinodular goitre had a relapse within the first year after stopping medication. [15]

AIMS OF INTERVENTION To eliminate the symptoms of hyperthyroidism and maximise quality of life, with minimum adverse effects of treatment.

OUTCOMES Change of state from hyperthyroid to euthyroid/hypothyroid; quality of life and neuropsychological impairments (evaluated by cognitive function tests, memory tests, reaction time, self-rating mood scales, and depression scores); CVD (episodes of atrial fibrillation and ischaemic events); cardiac function (evaluated by echocardiography); changes in body composition (obesity and bone mineral density measured by osteodensitometry or bioimpedance); changes in ophthalmopathy/eye symptoms; prevention of progression from subclinical to overt hyperthyroidism; levels of T4, T3, TSH; adverse effects of treatments (bone mass, fracture rate, development of hypothyroidism).

METHODS *BMJ Clinical Evidence* search and appraisal June 2007. The following databases were used to identify studies for this review: Medline 1966 to June 2007, Embase 1980 to June 2007, and The Cochrane Database of Systematic Reviews and Cochrane Central Register of Controlled Clinical Trials 2007, Issue 2. Additional searches were carried out using these websites: NHS Centre for Reviews and Dissemination (CRD) — for Database of Abstracts of Reviews of Effects (DARE) and Health Technology Assessment (HTA), Turning Research into Practice (TRIP), and NICE. Abstracts of the studies retrieved from the initial search were assessed by an information specialist. Selected studies were then sent to the author for additional assessment, using pre-determined criteria to identify relevant studies. Study-design criteria for inclusion in this review were: published systematic reviews and RCTs in any language, at least single blinded, and containing more than 20 individuals, no lower percentage of individuals followed up, but a minimum length of follow-up of 12 months. We excluded all studies described as “open”, “open label”, or not blinded unless blinding was impossible. We also searched for prospective cohort studies with a control group for the question on surgical treatments, and did a specific harms search for thyroid ophthalmopathy worsened by radioiodine or surgery. In addition, we use a regular surveillance protocol to capture harms alerts from organisations such as the FDA and the UK Medicines and Healthcare products Regulatory Agency (MHRA), which are added to the reviews as required. We have performed a GRADE evaluation of the quality of evidence for interventions included in this review (see table, p 12).

QUESTION What are the effects of drug treatments for primary hyperthyroidism?

OPTION ANTITHYROID DRUGS (CARBIMAZOLE, PROPYLTHIOURACIL, AND THIAMAZOLE) FOR PRIMARY HYPERTHYROIDISM

Relapse rates

Different durations of antithyroid treatments compared Treatment for 18 months with higher doses of carbimazole in people with Graves' hyperthyroidism may be more effective than 6 months' treatment at reducing the proportion of people who relapse at 18 months (low-quality evidence).

High doses compared with low doses High doses of thiamazole may be no more effective at 12 months at reducing the proportion of people who relapse or become euthyroid (low-quality evidence).

Antithyroid drugs alone (titration) compared with antithyroid drugs plus thyroxine (block-replace) Antithyroid drugs alone may be as effective in reducing the proportion of people with Graves' hyperthyroidism who relapse at 12–24 months (moderate-quality evidence).

Adverse effects

Antithyroid drugs alone (titration) compared with antithyroid drugs plus thyroxine (block-replace) Titration causes fewer rashes and is less likely to increase the proportion of people who withdraw from treatment because of adverse effects (high-quality evidence). Antithyroid drugs are associated with bone-marrow suppression, neutropenia, and agranulocytosis.

Note

We found no direct information about whether antithyroid drug treatment is better than no active treatment in people with hyperthyroidism, as conducting an RCT would be unethical; there is consensus that treatment is beneficial. We found no clinically important results comparing antithyroid drugs (carbimazole, propylthiouracil, or thiamazole) with each other.

For GRADE evaluation of interventions for hyperthyroidism, see table, p 12 .

Benefits:

Antithyroid drugs versus placebo:
We found no RCTs comparing carbimazole, thiamazole, or propylthiouracil with placebo in people with hyperthyroidism, although there is consensus that treatment is beneficial (see comment below).

Antithyroid drugs versus each other:
We found no systematic review or RCTs.

Antithyroid drugs versus radioiodine or surgery:
We found no systematic review or RCTs.

Duration of antithyroid treatment:
We found one systematic review (search date 2004, 4 RCTs, 390 people with Graves' hyperthyroidism). [16] It found that significantly fewer people relapsed with 18 months' treatment compared with 6 months' treatment with carbimazole 60 mg daily (1 RCT; 17/46 [37%] with 18 months' treatment *v* 28/48 [58%] with 6 months' treatment; RR 0.63, 95% CI 0.41 to 0.99). However, the review found no significant difference in relapse between more than 18 months' treatment compared with 12–18 months with carbimazole 30–50 mg daily (2 RCT; 38/86 [44%] with more than 18 months' treatment *v* 50/100 [50%] with 12-18 months' treatment; RR 0.88, 95% CI 0.67 to 1.16). The systematic review did not define relapse.

Dose of antithyroid therapy:
One RCT found no significant difference in the proportion of people who relapsed between thiamazole 10 mg daily compared with 40 mg daily for 12 months (36% with 10 mg/day *v* 37% with 40 mg/day; P value not reported). [17] The RCT also reported the proportion of people who were euthyroid at 3 and 6 weeks (3 weeks: 68% with 10 mg/day *v* 83% with 40 mg/day; 6 weeks: 85% with 10 mg/day *v* 92% with 40 mg/day).

Antithyroid drugs alone (titration) versus antithyroid drugs plus thyroxine (block-replace):
See benefits of antithyroid drugs plus thyroxine, p 7 .

Harms:

Duration of antithyroid treatment:
The review reported rates of rashes in people taking carbimazole and thiamazole (total number of RCTs assessed not reported: 49/722 [7%] with carbimazole *v* 82/714 [12%] with thiamazole; significance not reported). [16] The review did not report on hypothyroidism. One retrospective cohort study found similar rates of agranulocytosis after thiamazole and propylthiouracil (93/26,435 [0.35%] with thiamazole *v* 16/4373 [0.37%] with propylthiouracil; significance not reported). [18] One non-systematic review found that the adverse effects of thiamazole and carbimazole were dose related, whereas those of propylthiouracil were less clearly related to dose. [19] Minor adverse effects such as cutaneous reactions, arthralgia, and gastrointestinal upset occurred in about 5% of people taking antithyroid drugs. People taking antithyroid drugs can be switched from one antithyroid drug to another; however, about 50% of people who are unable to tolerate one drug will have adverse effects

with a second drug. [19] Hepatotoxicity was seen in 0.1–0.2% of people. Rare adverse effects such as vasculitis, cholestasis, and hypoglycaemia have been described.

Dose of antithyroid therapy:
One RCT found that 1/251 (0.4%) had granulocytopenia with thiamazole 10 mg daily, 1/258 (0.4%) had agranulocytosis with 40 mg daily; and 1/258 (0.4%) had pancytopenia with 40 mg daily. [17]

Antithyroid drugs alone (titration) versus antithyroid drugs plus thyroxine (block-replace):
See harms of antithyroid drugs plus thyroxine, p 7 .
Drug safety alert:
A drug safety alert has been issued on the risk of serious liver injury, including liver failure and death, associated with propylthiouracil (http://www.fda.gov/Drugs/DrugSafety).

Comment: Placebo-controlled trials would be considered unethical. Antithyroid drugs have been used for over 50 years, and there is consensus that they are effective. Carbimazole is a pro-drug of thiamazole. There have been concerns about bone-marrow suppression, neutropenia, and agranulocytosis with antithyroid drugs. [20] Advice includes asking people taking antithyroid drugs to report infection (especially sore throat); white blood cell count at any sign of infection; and stopping antithyroid drugs if there is clinical or laboratory evidence of neutropenia. The doses of antithyroid drugs reported in the studies are higher than generally used in practice. [20]

Clinical guide:
Antithyroid-drug treatment is often used as first-line treatment in Graves' disease and to render euthyroidism in nodular goitre and before radioiodine in Graves' disease. If allergy is present, people can be switched from one antithyroid drug to another.

OPTION RADIOACTIVE IODINE FOR PRIMARY HYPERTHYROIDISM

Ophthalmopathy
Compared with other treatments Radioactive iodine worsens ophthalmopathy in people with Graves' disease compared with medical treatment, surgery, or when combined with corticosteroids or thiamazole (high-quality evidence).

Note
We found no direct information about whether radioactive iodine is better than no active treatment in people with hyperthyroidism, as conducting an RCT would be unethical; there is consensus that treatment is likely to be beneficial. Radioiodine may increase some thyroid and extrathyroid cancers, but not the overall incidence of cancer.

For GRADE evaluation of interventions for hyperthyroidism, see table, p 12 .

Benefits: We found no systematic review or RCTs comparing radioactive iodine treatment with placebo, antithyroid drugs, or surgery in people with hyperthyroidism, although there is consensus that treatment is likely to be beneficial (see comment below).

Harms:

Cancer:
We found two retrospective cohort studies. [21] [22] The first cohort study (10,552 people given a therapeutic dose of radioiodine for hyperthyroidism; mean follow-up 15 years, range 0–30 years) calculated standard mortality rates (SMR) and found a increased risk ratio over time of gastric cancer associated with radioiodine treatment (SMR 1.41; P value not reported), but it found no increased total risk of cancer. [21] The second cohort study (7417 people treated with radioiodine for hyperthyroidism over 72,073 person-years of follow-up) found that observed cancer mortality was significantly less than expected cancer mortality (observed cancer deaths: 448, expected: 499; SMR 0.90, 95% CI 0.82 to 0.98). [22] However, it found that the incidence and mortality of small-bowel and thyroid cancers was significantly greater (small bowel: 6 diagnoses observed/1.2 expected; 6 deaths observed/0.8 expected; standardised incidence ratio 4.81, 95% CI 2.16 to 10.72; SMR 7.03, 95% CI 3.16 to 15.66]; thyroid: 9 diagnoses observed/2.8 expected; 5 deaths observed/1.8 expected; standardised incidence ratio 3.25, 95% CI 1.69 to 6.25; SMR 2.78, 95% CI 1.16 to 6.67).

Worsening of ophthalmopathy in people with Graves' disease:
We found two RCTs evaluating the influence of radioiodine on ophthalmopathy in people with Graves' disease. [23] [24] The first RCT (114 people randomised to radioiodine, surgery, or medical antithyroid treatment for hyperthyroidism caused by Graves' disease) found that ophthalmopathy worsened in significantly more people with radioiodine than with surgery or medical treatment (13/39 [33%] with radioiodine *v* 6/37 [16%] with surgery *v* 4/38 [10%] with medical treatment; P less than 0.02 for radioiodine *v* surgery or medical combined). [24] The second RCT (443 people with Graves' hyperthyroidism and mild or no ophthalmopathy) found that ophthalmopathy worsened in significantly more people at 2–6 months with radioiodine than with radioiodine plus corticosteroids or with thiamazole (23/150 [15%] with radioiodine *v* 0/145 [0%] with radioiodine plus corticosteroids

v 4/148 [3%] with thiamazole; P less than 0.001 for radioiodine *v* radioiodine plus corticosteroids, P less than 0.001 for radioiodine *v* thiamazole, between-group comparison not reported). [23]

Transition of nodular toxic goitre to autoimmune hyperthyroidism:
One observational study found 6/149 (4%) of consecutive people with nodular toxic goitre developed radioiodine-induced Graves'-like syndrome. [25]

Comment: A placebo-controlled trial of radioiodine in people with hyperthyroidism would be considered unethical. Several studies have evaluated the effect of different doses.

Clinical guide:
Using high doses of radioiodine induces a high percentage of cure defined as euthyroidism or hypothyroidism and low frequency of persistent hyperthyroidism. A low initial incidence of hypothyroidism will inevitably be at the expense of a rise in the proportion of people with persistent hyperthyroidism. [26] In the USA, people with hyperthyroidism are generally given a high dose of radioiodine and then thyroxine to prevent hypothyroidism. However, in Europe, a dose of radioiodine is given to cure hyperthyroidism so that the person is euthyroid.

OPTION ADDING ANTITHYROID DRUGS (CARBIMAZOLE, PROPYLTHIOURACIL, AND THIAMAZOLE) TO RADIOACTIVE IODINE TREATMENT FOR PRIMARY HYPERTHYROIDISM (LESS EFFECTIVE THAN RADIOACTIVE IODINE ALONE) New

Treatment success
Antithyroid drugs plus radioactive iodine compared with radioactive iodine alone Adding antithyroid drugs to radioactive iodine may be less effective than using radioactive iodine alone at decreasing the proportion of people with persistent or recurrent hyperthyroidism, or at reducing the need for further treatment. However, antithyroid drugs (given a week after radioiodine) plus radioiodine may reduce rates of hypothyroidism (low-quality evidence).

Adverse effects
Adding antithyroid drugs to radioactive iodine has been associated with lower rates of new-onset atrial fibrillation and death compared with radioiodine alone.

For GRADE evaluation of interventions for hyperthyroidism, see table, p 12 .

Benefits: **Antithyroid drugs plus radioactive iodine versus radioactive iodine alone:**
We found one systematic review (search date 2006, 14 RCTs, 1306 people with hyperthyroidism) comparing radioactive iodine treatment plus antithyroid drugs versus radioactive iodine alone. [27] The RCTs used the following antithyroid drugs, given in the week before or after radioiodine treatment: carbimazole (3 RCTs), propylthiouracil (4 RCTs), and thiamazole (6 RCTs); and one RCT had an additional treatment arm and used both propylthiouracil and thiamazole. The review reported that the quality of the methods of the included RCTs was low, with few RCTs giving enough information about randomisation or allocation concealment.

Treatment failure: The review found that overall, rates of treatment failure (defined as persistent or recurrent hyperthyroidism or need for further treatment) were significantly higher after antithyroid drug plus radioiodine treatment compared with radioiodine treatment alone (14 RCTs: 235/713 [33%] with antithyroid drug plus radioiodine *v* 171/729 [23%] with radioiodine alone; RR 1.29, 95% CI 1.07 to 1.52; P = 0.006 with intention-to-treat analysis; RR 1.34, 95% CI 0.96 to 1.88; P = 0.09 with per-protocol analysis). Subgroup analysis found that, compared with radioiodine alone, adjuvant antithyroid treatment increased failure rates whether given in the week before radioiodine therapy (77/271 [28%] with antithyroid drug plus radioiodine *v* 55/294 [19%] with radioiodine alone; RR 1.48, 95% CI 1.09 to 2.00; P = 0.01) or in the week after radioiodine therapy (103/267 [39%] with antithyroid drug plus radioiodine *v* 83/275 [30%] with radioiodine alone; RR 1.32, 95% CI 1.04 to 1.68; P = 0.03). [27]
Hypothyroidism: The review found that overall, adding antithyroid drugs to radioiodine treatment significantly reduced rates of hypothyroidism compared with radioiodine alone (14 RCTs, 1306 people: 130/713 [18%] with antithyroid drugs plus radioiodine *v* 208/729 [29%] with radioiodine alone; RR 0.68, 95% CI 0.53 to 0.87, P = 0.0006, intention-to-treat analysis). Subgroup analysis found that this reduction was not significant when adjuvant antithyroid drugs were given in the week before radioiodine treatment (RR 0.76, 95% CI 0.57 to 1.01; P = 0.06), but was significant when adjuvant antithyroid drugs were given in the week after radioiodine treatment (RR 0.57, 95 % CI 0.41 to 0.78; P less than 0.001). [27] The review stated that there was no difference in summary estimates for different antithyroid drugs.

Harms: **Antithyroid drugs plus radioactive iodine versus radioactive iodine alone:**
Adverse effects with adjuvant antithyroid drugs — mainly allergic skin reactions to thimazole — were reported in 12/660 (2%) of people. Adjuvant antithyroid drugs were associated with reduced thyroid

hormone concentrations for between 7–12 weeks after radioiodine treatment, and lower rates of new-onset atrial fibrillation and death (atrial fibrillation: 1/660 [0.2%] with antithyroid drugs plus radioiodine *v* 3/646 [0.5%] with radioiodine alone; death: 1/660 [0.2%] with antithyroid drugs plus radioiodine v 6/646 [0.9%] with radioiodine alone; P values and significance not reported). [27]

See also harms of antithyroid drugs, p 3 .

Comment: The review did not draw firm conclusions about the optimal interruption period of antithyroid drugs for the people undergoing radioiodine treatment (to avoid both relapse of hyperthyroidism and cardiovascular complications).

Clinical guide:
In people with severe hyperthyroidism, adjuvant antithyroid treatment can be used to stabilise the person, but should be discontinued approximately 1 week before and after radioiodine treatment to avoid treatment failure of the radioiodine.

OPTION ANTITHYROID DRUGS (CARBIMAZOLE, PROPYLTHIOURACIL, AND THIAMAZOLE) PLUS THYROXINE FOR PRIMARY HYPERTHYROIDISM

Relapse rates
Antithyroid drugs plus thyroxine (block-replace) compared with antithyroid drugs alone (titration) Block-replace regimens of antithyroids plus thyroxine seem no more effective than titration regimens of antithyroids alone in reducing the proportion of people with Graves' hyperthyroidism who relapse at 12–24 months (moderate-quality evidence).

Initial antithyroid drugs followed by thyroxine compared with initial antithyroid drugs followed by no treatment Initial antithyroid drugs followed by thyroxine may be no more effective at reducing relapses in people with Graves' hyperthyroidism (low-quality evidence).

Adverse effects
Antithyroid drugs plus thyroxine (block-replace) compared with antithyroid drugs alone (titration) Block-replace causes more rashes and is more likely to increase the proportion of people who withdraw from treatment because of adverse effects (high-quality evidence).

For GRADE evaluation of interventions for hyperthyroidism, see table, p 12 .

Benefits:

Antithyroid drugs plus thyroxine (block-replace) versus antithyroid drugs alone (titration):
We found one systematic review (search date 2004, 12 RCTs, 1250 people with Graves' hyperthyroidism), which compared a block-replace regimen of antithyroid drugs (carbimazole, propylthiouracil, or thiamazole) plus thyroxine or triiodothyronine versus antithyroid drugs alone. [16] It found no significant difference in the proportion of people relapsing at 12–24 months between block-replace and titration regimens (322/636 [51%] with block-replace *v* 332/614 [54%] with titration; RR 0.93, 95% CI 0.84 to 1.03). The review did not report on improvement in symptoms, or on initial treatment success in reverting to euthyroidism; nor did it define relapse.

Initial antithyroid drugs followed by either thyroxine or no treatment:
We found one systematic review (search date 2004, 4 RCTs, 566 people with Graves' hyperthyroidism). [16] It found no significant difference in relapse between initial antithyroid drugs followed by thyroxine and initial antithyroid drugs followed by no treatment (RR 1.09, 95% CI 0.86 to 1.39).

Antithyroid drugs plus thyroxine (block-replace) versus radioiodine or surgery:
We found no systematic review or RCTs.

Harms:

Antithyroid drugs plus thyroxine (block-replace) versus antithyroid drugs alone (titration):
The systematic review found that there were significantly more rashes with block-replace compared with titration (7 RCTs; 63/616 [10%] with block-replace *v* 31/622 [5%] with titration; RR 2.04, 95% CI 1.35 to 3.06). [16] It also found that the proportion of people who withdrew because of adverse effects was significantly higher with block-replace (4 RCTs; 58/353 [16%] with block-replace *v* 30/344 [9%] with titration; RR 1.89, 95% CI 1.25 to 2.85). The block-replace regimens also had more people with agranulocytosis compared with the titration group (9 with block-replace *v* 3 with titration; no further data reported).

See also harms of antithyroid drugs, p 3 .

Initial antithyroid drugs followed by either thyroxine or no treatment:
The systematic review gave no information on adverse effects. [16]

Comment: In the systematic review, the doses of thiamazole used for block-replace were high (60–80 mg/day) in several of the RCTs, and thus higher than used in low-dose block-replace treatment (typically 20 mg/day). [16] This may account for the finding of more adverse effects with block-replace treatment in high-dose compared with monotherapy (low dose).

Clinical guide:
Block-replace treatment can be used if it is difficult to render euthyroidism on titration regime.

QUESTION What are the effects of surgical treatments for primary hyperthyroidism?

OPTION THYROIDECTOMY

Treatment success
Total thyroidectomy compared with subtotal thyroidectomy Total thyroidectomy may be more effective at reducing the proportion of people with Graves' disease who have persistent or recurring hyperthyroidism, and at increasing the proportion of people who become hypothyroid or euthyroid (low-quality evidence).

Ophthalmopathy
Total thyroidectomy compared with subtotal thyroidectomy Total, bilateral subtotal thyroidectomy, and unilateral total thyroidectomy plus contralateral subtotal thyroidectomy seem equally effective at increasing the proportion of people with an improvement in Graves' ophthalmopathy (moderate-quality evidence).

Note
We found no direct information about whether surgery is better than no active treatment, antithyroid drugs, or radioiodine in people with hyperthyroidism; there is consensus that treatment is beneficial.

For GRADE evaluation of interventions for hyperthyroidism, see table, p 12 .

Benefits:

Thyroidectomy versus placebo:
We found no systematic review or RCTs comparing surgery with placebo in people with hyperthyroidism, although there is consensus that treatment is beneficial.

Thyroidectomy versus antithyroid drugs or radioiodine:
We found no systematic review or RCTs.

Total thyroidectomy versus subtotal thyroidectomy:
We found one systematic review [28] and one subsequent RCT. [29] The systematic review (search date 1998; 35 studies [study types not reported], 7241 people with Graves' disease) found that hyperthyroidism persisted or recurred in 0% of people with total thyroidectomy compared with 8% (numbers not reported; analysis not by intention to treat) of people with subtotal thyroidectomy at 4 months to 32 years (significance assessment not performed). [28] It also found that more people became hypothyroid or euthyroid after total thyroidectomy compared with subtotal thyroidectomy (100% hypothyroid after total thyroidectomy *v* 26% hypothyroid/60% euthyroid after subtotal thyroidectomy; significance assessment not performed). The purpose of the second subsequent RCT was to evaluate the effect of thyroid surgery on Graves' ophthalmopathy. It compared three types of thyroidectomy in 150 people with Graves' disease: total thyroidectomy, bilateral subtotal thyroidectomy (total remnant less than 4 mL), and unilateral total thyroidectomy plus contralateral subtotal thyroidectomy (remnant less than 4 mL). [29] Preoperative medical treatment was either antithyroid drugs, beta-blockers, both, or no medical treatment. It found no significant difference between the three groups in the proportion of people whose Graves' ophthalmopathy improved (22/31 [71%] with total thyroidectomy *v* 21/29 [72%] with bilateral subtotal thyroidectomy *v* 20/29 [69%] with total unilateral plus subtotal contralateral thyroidectomy ; P greater than 0.05 among groups). Two thirds of people had Graves' ophthalmopathy (98/150 [65%]), and of these 61/98 (62%) had documented improvement of their eye symptoms (71% with total thyroidectomy *v* 74% with bilateral subtotal thyroidectomy *v* 74% with total unilateral plus subtotal contralateral thyroidectomy; reported as not significant among groups).

Harms:

Thyroidectomy versus placebo:
We found no RCTs.

Total thyroidectomy versus subtotal thyroidectomy:
The systematic review found no significant difference in permanent recurrent laryngeal nerve injury between total and subtotal thyroidectomy (0.9% with total thyroidectomy *v* 0.7% with subtotal thyroidectomy; absolute numbers not reported; P greater than 0.05). [28] It also reported that there were no perioperative mortalities from thyroid storm. The review found no permanent recurrent laryngeal nerve palsy. It also reported that there were no postoperative mortalities. The subsequent

RCT found no significant difference in permanent recurrent laryngeal nerve paralysis among total thyroidectomy, bilateral subtotal thyroidectomy, and total unilateral plus contralateral subtotal thyroidectomy (0/49 [0%] with bilateral subtotal thyroidectomy *v* 1/54 [1.9%] with total unilateral plus subtotal contralateral thyroidectomy *v* 1/47 [2.1%] with total thyroidectomy; reported as not significant). [29] It found that early postoperative hypoparathyroidism was significantly different in a between-group comparison of total versus either bilateral subtotal or total unilateral plus subtotal contralateral thyroidectomy (14/47 [30%] with total thyroidectomy *v* 5/49 [10%] with bilateral subtotal thyroidectomy *v* 3/54 [6%] with total unilateral plus subtotal contralateral thyroidectomy; P = 0.002 for total thyroidectomy *v* other procedures). There was no significant difference among groups in rates of permanent hypoparathyroidism (5/47 [11%] with total thyroidectomy *v* 2/49 [4%] with bilateral subtotal thyroidectomy *v* 1/54 [2%] with total unilateral plus subtotal contralateral thyroidectomy ; reported as not significant). It also found no significant difference in wound infection among groups (2/47 [4%] with total thyroidectomy *v* 1/49 [2%] with bilateral subtotal thyroidectomy *v* 2/54 [4%] with total unilateral plus subtotal contralateral thyroidectomy ; reported as not significant). It found similar reductions between groups in Graves' ophthalmopathy score (American Thyroid Association scale, 0 = best, 40 = worst; –2.5 with bilateral subtotal thyroidectomy *v* –2.0 with total unilateral plus subtotal contralateral thyroidectomy *v* –2.0 with total thyroidectomy; reported as not significant). Postoperative endocrine ophthalmopathy was found in 5/57 (9%) of people who did not have preoperative Graves' ophthalmopathy (data for each group not reported, reported as no significant difference between “total and subtotal thyroidectomy”).

Comment: Placebo-controlled trials of surgery in people with hyperthyroidism would be considered unethical.

Clinical guide:
Surgery is often used for people with large goitres.

QUESTION What are the effects of treatments for subclinical hyperthyroidism?

OPTION ANTITHYROID TREATMENT FOR SUBCLINICAL HYPERTHYROIDISM

Treatment success
Radioiodine compared with no antithyroid treatment Radioiodine may be more effective at 2 years at increasing thyroid-stimulating hormone levels, and at lowering free T4 and T3 levels within normal ranges in postmenopausal women with no compression symptoms from nodular goitre (very low-quality evidence).

Note
We found no direct information assessing antithyroid drugs (carbimazole, propylthiouracil, and thiamazole) in people with subclinical hyperthyrodism.

For GRADE evaluation of interventions for hyperthyroidism, see table, p 12 .

Benefits:

Radioactive iodine:
We found one controlled clinical trial (CCT; 28 postmenopausal women with nodular goitre with free thyroxine (T4) and triiodothyronine (T3) estimates within the normal range [range not reported] and low thyroid-stimulating hormone [TSH, also known as thyrotropin] [less than 0.20 mU/L]). [30] People with compression symptoms from the goitre (16 women) were given radioactive iodine; women who did not have compression symptoms from the goitre (12 women) were given no antithyroid treatment. The CCT found that TSH was significantly higher at 2 years in women with radioactive iodine compared with women without antithyroid treatment (0.390 mU/L with radioiodine *v* 0.023 mU/L with no treatment; P less than 0.001). It also found that both spine and hip bone mineral densities (BMD) were significantly higher at 2 years with radioiodine compared with no treatment (spine BMD: 102% of initial BMD with radioiodine *v* 96% of initial BMD with no treatment; P less than 0.02; hip BMD: 102% of initial BMD with radioiodine *v* 98% of initial BMD with no treatment; P less than 0.01). The free T4 and T3 levels were within normal range in both groups before and after treatment. In the radioiodine-treated group, free T4 and free T3 declined significantly (in the normal range), free T4 index (normal range 62–158 arbitrary units) declined from 102 arbitrary units to 80 arbitrary units (P less than 0.02), free T3 index (normal range 0.84–2.8 arbitrary units) declined from 2.03 arbitrary units to 1.58 arbitrary units (P less than 0.01). The CCT gave no information on clinical outcomes.

Antithyroid drugs (carbimazole, propylthiouracil, and thiamazole):
We found no systematic review or RCTs.

Harms:

Radioactive iodine:
The CCT gave no information on adverse effects. [30]

Other antithyroid drugs (carbimazole, propylthiouracil, and thiamazole):
We found no RCTs. See also harms reported for radioiodine, p 5 and antithyroid drugs, p 3 .

Comment: The women in the CCT were not randomised, but the indication of treatment was compression symptoms of goitre and not thyroid function or symptoms of hyperthyroidism. [30]

Clinical guide:
Theoretically, the treatment of subclinical hyperthyroidism could induce hypothyroidism; however, we found no RCT which evaluated this.

GLOSSARY

Titration regimen Antithyroid treatment as monotherapy to try and reach a euthyroid state.
Block-replace treatment Combination of antithyroid treatment and concomitant thyroid-replacement therapy.
High-quality evidence Further research is very unlikely to change our confidence in the estimate of effect.
Low-quality evidence Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Moderate-quality evidence Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Very low-quality evidence Any estimate of effect is very uncertain.

SUBSTANTIVE CHANGES

Adding antithyroid drugs (carbimazole, propylthiouracil, and thiamazole) to radioactive iodine treatment for primary hyperthyroidism New option with one systematic review, [27] which found that antithyroid drugs given in the week before or after radioactive iodine therapy increased treatment failure compared with radioactive iodine alone, although it reduced hypothyroidism. Categorised as Unlikely to be beneficial.

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Disclaimer

TABLE **GRADE evaluation of interventions for hyperthyroidism**

Important outcomes	**Treatment success, relapse, neuropsychological impairments, CVD, changes in parameters of thyroid function, changes in ophthalmology, quality of life, adverse effects**								
Number of studies (participants)	**Outcome**	**Comparison**	**Type of evidence**	**Quality**	**Consistency**	**Directness**	**Effect size**	**GRADE**	**Comment**
What are the effects of drug treatments for primary hyperthyroidism?									
3 (280) [16]	Relapse	Different durations of antithyroid treatments compared	4	0	0	−2	0	Low	Consistency point deducted for different results at different endpoints, but added for dose response. Directness points deducted for not defining outcome and for using higher doses than would be used in practice
1 (309) [17]	Relapse	Different doses of thiamazole compared	4	−1	0	−1	0	Low	Quality point deducted for incomplete reporting of results. Directness point deducted for using higher doses than would normally be used in practice
1 (309) [17]	Treatment success	Different doses of thiamazole compared	4	−1	0	−1	0	Low	Quality point deducted for incomplete reporting of results. Directness point deducted for using higher doses than would normally be used in practice
2 (557) [24] [23]	Ophthalmopathy	Radioiodine *v* surgery/medical treatment/radioiodine plus corticosteroids or thiamazole	4	0	0	0	0	High	
14 (1442) [27]	Treatment sucess	Antithyroids plus radioiodine *v* radioiodine alone	4	−2	0	0	0	Low	Quality points deducted for poor methodology and uncertainty about randomisation/concealment
12 (1250) [16]	Relapse rates	Antithyroid drugs plus thyroxine (block-replace) *v* antithyroid drugs alone (titration)	4	0	0	−1	0	Moderate	Directness point deducted for not defining outcome
4 (566) [16]	Relapse rates	Initial antithyroid drugs followed by thyroxine *v* initial antithyroid drugs followed by no treatment	4	−1	0	−1	0	Low	Quality point deducted for incomplete reporting of results. Directness point deducted for not defining outcome
11 (1935) [16]	Adverse effects	Antithyroid drugs plus thyroxine (block-replace) *v* antithyroid drugs alone (titration)	4	0	0	0	0	High	
What are the effects of surgical treatments for primary hyperthyroidism?									
35 studies (study type not reported) (7241) [28]	Treatment success	Total thyroidectomy *v* subtotal thyroidectomy	4	–2	0	0	0	Low	Quality points deducted for incomplete reporting of results and for no intention-to-treat analysis
1 (89) [29]	Ophthalmopathy	Total thyroidectomy *v* subtotal thyroidectomy	4	–1	0	0	0	Moderate	Quality point deducted for sparse data
What are the effects of treatments for subclinical hyperthyroidism?									
1 CCT (28) [30]	Treatment success	Radioiodine *v* no antithyroid treatment	4	–3	0	0	0	Very low	Quality points deducted for sparse data, CCT, and lack of randomisation

Important out-comes	Treatment success, relapse, neuropsychological impairments, CVD, changes in parameters of thyroid function, changes in ophthalmology, quality of life, adverse effects								
Number of studies (participants)	**Outcome**	**Comparison**	**Type of evidence**	**Quality**	**Consis-tency**	**Direct-ness**	**Effect size**	**GRADE**	**Comment**

Type of evidence: 4 = RCT; 2 = Observational; 1 = Non-analytical/expert opinion. Consistency: similarity of results across studies
Directness: generalisability of population or outcomes
Effect size: based on relative risk or odds ratio