

### New drugs

Editor, - John Watson's professor of old, ('Letters' Aust Prescr 1999;22:77) used an important dictum about using new and old drugs, but he could not claim originality. I thought it was a paraphrase of a couplet in Polonius's advice to Laertes (Hamlet, by William Shakespeare) and my doctor brother Michael thought it was from Sir William Osler. The latter probably would have invented it if it had not been originally phrased by Pope, in his Essay on Criticism (lines 335-6):

'Be not the first by whom the new are tried  
Nor yet the last to lay the old aside'.

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### Sertraline and statins

Editor, - Two issues arise from Vol 22, No. 5. The article by John Tiller 'The new antidepressants - clinical applications'

(Aust Prescr 1999;22:108-11) omits reference to sertraline as an agent approved for treatment of panic disorder. Panic disorder has been an approved indication for sertraline since December 1997.

In the article by Eve Hurley 'Assessing the statins' (Aust Prescr 1999;22:114-7) the self-test question 8, about primary prevention, correctly answered as 'true', could amount to less than the 'whole truth'. I suggest it would be more accurate to say that, based on studies reported to date, there is more evidence of benefit from statins in secondary prevention than there is in primary prevention (i.e. three trials versus one published to date). The statement offered is too absolute, and might get a pharmaceutical company into trouble with the Code of Conduct Committee if offered for promotional purposes.

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## Managing subclinical hypothyroidism

In a patient with overt primary hypothyroidism, management is usually straightforward: treatment with thyroxine should be offered to anyone with characteristic clinical features, a raised serum thyroid stimulating hormone (TSH) concentration and a low serum thyroxine (T4) concentration. More difficult is the management of a patient with subclinical hypothyroidism, in whom serum TSH is raised but T4 level is normal, and who is either asymptomatic or has only non-specific symptoms. Left untreated, some of these patients will eventually develop overt hypothyroidism. Here we discuss the use of thyroxine in patients with subclinical hypothyroidism.

### Background

#### What is subclinical hypothyroidism?

Patients are described as having subclinical hypothyroidism when their serum concentrations of T4 and triiodothyronine (T3) are normal, the serum TSH concentration is raised (i.e. above the typical reference range 0.5-5 mU/L) and they have no specific symptoms or signs of thyroid dysfunction. Many with these features will have had hyperthyroidism and developed hypothyroidism following treatment given to destroy the function of the overactive thyroid gland. Most, however, will be diagnosed after investigation of non-specific symptoms, such as tiredness or weight gain.

#### Prevalence

Spontaneous subclinical hypothyroidism is more common in women and the incidence increases with age and is associated with the presence of antithyroid antibodies. However, serum

TSH concentrations do not increase as a direct result of ageing in women or men. In community surveys, around 10% of women over 55-60 years of age have been found to have a serum TSH concentration over 5 or 6 mU/L.<sup>1-3</sup> Although subclinical hypothyroidism can develop spontaneously, the condition is more common in patients who have been treated for hyperthyroidism with either iodine-131 or surgery, and in those with organ-specific autoimmune diseases such as pernicious anaemia, insulin-dependent diabetes mellitus or Addison's disease.

#### Natural history of subclinical hypothyroidism

In a community survey of 2779 patients in the U.K., in which patients were followed up after 20 years, women with subclinical hypothyroidism were more likely to develop overt hypothyroidism if they had antibodies to the enzyme microsomal thyroid peroxidase.<sup>4</sup> The annual rate of progression in women was 4.3% if TSH was above 6 mU/L and thyroid peroxidase antibodies were detected, 2.6% if the serum TSH concentration alone was raised, and 2.1% if antibodies were present but the serum TSH concentration was normal. Men were less commonly affected by subclinical hypothyroidism than women but more likely to experience disease progression.<sup>4</sup> The risk of developing hypothyroidism within 20 years increased with the initial serum TSH level: 1% where it was 2.5 mU/L (in antithyroid-antibody negative patients); 4% where it was 5.0 mU/L. Progression to overt hypothyroidism is also more common when the patient is over 60 years old<sup>5</sup> or when the serum TSH concentration is raised following iodine-131 therapy.<sup>6</sup>

## Definition of normal range

There is no absolute threshold between hypothyroidism and euthyroidism. However, because calculation of the accepted reference range (0.5 to 5-6 mU/L) probably includes some people with mild thyroid failure, the true upper limit of normal TSH concentration is likely to be lower than 5-6 mU/L.

## Why start thyroxine?

### *Effect on symptoms*

In a double-blind study, 33 women, previously treated for hyperthyroidism, with serum TSH concentrations greater than 3.5 mU/L (a threshold below the accepted upper limit) and non-specific symptoms, were randomised to receive either placebo or thyroxine for one year. Symptoms improved in 47% of patients on thyroxine compared with 19% of those on placebo ( $p < 0.05$ ).<sup>7</sup> Another double-blind, cross-over study involved 20 women from the general population with serum TSH concentration greater than 4 mU/L and no symptoms of hypothyroidism: 4 of 17 women who completed the study improved during the 6-month thyroxine phase compared with the placebo phase, as judged by psychometric tests and their own rating of well being.<sup>8</sup>

### *Effect on blood lipids and cardiovascular disease*

Hypercholesterolaemia is a recognised feature of overt hypothyroidism, but it is not clear whether subclinical hypothyroidism contributes to the development of ischaemic heart disease.

A meta-analysis of 13 studies of intervention with thyroxine involving 278 patients with subclinical hypothyroidism indicated that thyroxine therapy, which reduced TSH levels to the normal range, decreased total plasma cholesterol by only 0.4 mmol/L, independently of the initial plasma level (i.e. an average 6% reduction in total cholesterol concentration).<sup>9</sup>

The results of a small, non-randomised, controlled study suggest that patients with hypercholesterolaemia who have already developed atherosclerotic disease may benefit from thyroxine. The study involved 31 women with intermittent claudication and raised TSH ( $>4$  mU/L); treatment with thyroxine for 1 year was associated with less morbidity and less progression of arterial disease than in an untreated group.<sup>10</sup> These benefits were associated with increased high density lipoprotein, reduced total cholesterol and reduced apo-B lipoprotein concentrations.

### *Effect on fertility*

A slightly raised serum TSH concentration, usually associated with autoimmune thyroid disease, is sometimes found in women undergoing investigation for infertility. Although there is no evidence that thyroxine treatment enhances the likelihood of conception, most doctors would probably correct any biochemical abnormality in order to provide as normal a hormonal environment for pregnancy as possible.

### *Effect on psychiatric disorders*

The use of thyroxine in patients with psychiatric symptoms and a raised TSH has not been assessed in clinical trials.

Despite this, treatment of thyroid dysfunction is often attempted in patients with treatment-resistant or recurrent depression.

## Safety of treatment

Treatment of subclinical hypothyroidism with thyroxine should not cause problems provided that serum TSH concentration is restored to within the reference range. Fine titration of the dose may be difficult because thyroxine tablets come in only 3 strengths. In patients recently treated for Graves' disease, fluctuations in the titre of TSH-receptor-stimulating antibodies can make titration of the thyroxine replacement dose difficult.<sup>11</sup>

### *Risk of osteoporosis*

There has been some concern that thyroxine given in doses that suppress serum TSH to undetectable concentrations might promote osteoporosis. Meta-analyses of various controlled studies in which thyroxine therapy has been (in some patients) excessive are difficult to interpret because of the heterogeneity of patients studied.<sup>12,13</sup> One meta-analysis suggests that postmenopausal women with serum TSH concentration suppressed to below the reference range have a higher annual bone loss than healthy individuals not given thyroxine<sup>12</sup>; another suggests that thyroxine therapy, even when adjusted to give a TSH value within the range, is associated with bone loss in premenopausal women.<sup>13</sup> However, a study of 1180 women (largely postmenopausal) on thyroxine for over 1 year found no increased rate of fracture when serum TSH concentration was suppressed to below 0.05 mU/L compared with those with a serum TSH concentration in the range 0.05-4 mU/L.<sup>14</sup>

It is likely that patients most at risk of developing osteoporosis from thyroxine therapy are those whose hypothyroidism has resulted from treatment of hyperthyroidism that might already have reduced bone mass. This view is supported by the results of a case-control study involving 148 women that examined the effect of previous thyroid history and thyroxine therapy on bone mineral density: thyroxine therapy alone did not represent a significant risk factor for loss of bone mineral density, but there was an increased risk of bone loss in postmenopausal (but not premenopausal) women with a previous history of thyrotoxicosis treated with radioiodine.<sup>15</sup> The risk of osteoporosis from thyroid replacement therapy has probably been overestimated.

### *Risk of atrial fibrillation*

There is concern that a low serum TSH concentration may be a risk factor for atrial fibrillation in older patients. In a study to examine this possibility, 2007 patients aged 60 years or more who did not have atrial fibrillation at baseline were observed for 10 years: the risk of developing atrial fibrillation was increased threefold in those with low serum TSH concentration (no higher than 0.1 mU/L), compared to those with normal TSH concentration. However, this study has been criticised because it included patients with overt hyperthyroidism, in whom serum T3 concentrations were almost certainly higher than those in patients taking thyroxine.<sup>16</sup>

## Management

Evidence of clinical benefit, though limited, broadly suggests that it is better to treat subclinical hypothyroidism before overt hypothyroidism develops. Such a strategy should reduce the risk of loss to follow-up and the subsequent morbidity of a delayed diagnosis of profound hypothyroidism.<sup>17</sup> In patients with only slightly raised TSH (less than 10 mU/L), without antithyroid antibodies, treatment may be deferred as the conversion rate to overt hypothyroidism is less than 3% per year.<sup>17</sup> Increased serum TSH concentration may be transient<sup>2</sup> and simply reflect a non-thyroidal illness or transient thyroiditis from which the patient is recovering, and so thyroxine should not be started on the basis of a single raised serum TSH concentration. Therefore, if serum TSH concentration is slightly raised in the absence of antithyroid antibodies, it is wise to repeat the measurement after about 3 months. The presence of antithyroid antibodies should reinforce the decision to treat. The presence of goitre or a family history of autoimmune thyroid disease does not predict the development of hypothyroidism<sup>4</sup> and should not be taken as a reason for starting thyroxine.

Occasionally, patients feel better on thyroxine replacement therapy only when serum TSH is reduced to below the reference range. This seems to occur when the dose of thyroxine is adjusted to bring the serum TSH concentration into, rather than below, the reference range. In this situation, several of our consultants recommend monitoring the T3 level to ensure that thyroxine replacement does not result in hyperthyroidism.

## Conclusion

Subclinical hypothyroidism, characterised by normal thyroxine (T4) with serum thyroid stimulating hormone (TSH) concentration raised above 5-6 mU/L, with or without non-specific symptoms, is common in middle-aged and older women. Treatment with thyroxine should be given to women and men with subclinical hypothyroidism in whom serum TSH concentration is raised and who have detectable levels of microsomal thyroid peroxidase antibodies. The aim of thyroxine therapy should be to restore serum TSH concentration to within the reference range: levels below this range are possibly associated with an increased risk of developing atrial fibrillation. A serum TSH concentration of less than 10 mU/L in patients who are antibody-negative warrants observation rather than immediate treatment as it may be a transient phenomenon.

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[M = meta-analysis; R = randomised controlled trial]

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