

# An overview of thyroid disorders and their management

G Schellack,<sup>1</sup> N Schellack,<sup>2</sup> C de Moura-Cunningham<sup>2</sup>

<sup>1</sup>Independent Consultant Pharmaceutical Industry, South Africa

<sup>2</sup>Department of Pharmacology, University of Pretoria, South Africa

Corresponding author, email: natalie.schellack@up.ac.za

## Abstract

Disorders of the thyroid gland are frequently encountered in the clinical practice setting and typically fall into one of two categories, namely hypothyroidism (i.e. deficient levels of circulating thyroid hormone), or hyperthyroidism (or thyrotoxicosis) that involves abnormally high levels of thyroid hormone in the blood stream. This article provides a high-level overview of thyroid function, the two major pathophysiological abnormalities of the thyroid gland, as well as treatment modalities aimed at managing patients with thyroid pathology. In addition, a brief description of two major autoimmune conditions of the thyroid gland, namely Graves' disease and Hashimoto's thyroiditis, is also provided.

**Keywords:** thyroid gland, thyroxine, triiodothyronine, iodide, hypothyroidism, hyperthyroidism, goitre, thyroid storm, Hashimoto's thyroiditis, Graves' disease, exophthalmos, cretinism, myxoedema

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## Introduction

Disorders of the thyroid gland are frequently encountered in the clinical practice setting and typically fall into one of two categories, namely hypothyroidism (i.e. deficient levels of circulating thyroid hormone), or hyperthyroidism (or thyrotoxicosis) that involves abnormally high levels of thyroid hormone in the bloodstream. The two thyroid hormones,  $T_3$  and  $T_4$ , play a vital role in a wide variety of body functions, with particular reference to normal growth, neurological and sexual development, as well as basal metabolism.

## Overview of thyroid pathophysiology

The thyroid gland forms part of the peripheral endocrine system (i.e. those endocrine glands that are situated *outside* of the central nervous system). It is characteristically shaped like a bowtie (or butterfly), with the central isthmus joining together its two lateral lobes. It is situated in the midline, anterior to the larynx and trachea, and at the level of the C5 to T1 vertebrae. The highly vascular thyroid gland secretes two blood-borne thyroid hormones that regulate the rate of the body's basal metabolism (including energy levels and body temperature), as well as calcitonin that opposes the net effect of parathyroid hormone (PTH) on plasma calcium levels, in the regulation of calcium metabolism. The thyroid hormones also play a vital role in normal growth and development, and can augment the functions and effects of the sympathetic nervous system.<sup>1-5</sup>

The two thyroid hormones, which are secreted by the follicular cells, are triiodothyronine ( $T_3$ ) and thyroxine (tetraiodothyronine or  $T_4$ ), which are both synthesised from tyrosine and iodine. Tyrosine is a non-essential amino acid that is synthesised in the body, and the iodine is derived from the diet (i.e. via food and water intake,

but could also be supplemented with medication). In the body, the negatively charged iodide ions ( $I^-$ ) are actively transported from the bloodstream, via the follicular cells, into the colloid of the thyroid gland against a steep concentration (electrochemical) gradient by the sodium-iodide-symporter.<sup>1-5</sup>

About 90% of the secreted  $T_4$  is converted to  $T_3$  in peripheral target tissues outside of the thyroid gland. This process of activation mainly takes place in the liver and kidneys.  $T_3$  is significantly more potent than  $T_4$ . Thyroid hormone secretion is regulated via the hypothalamic-pituitary-thyroid gland axis. Thyroid-stimulating hormone (TSH) from the anterior pituitary gland regulates the secretion of  $T_3$  and  $T_4$  into the bloodstream. In turn, TSH-secretion is regulated by thyrotropin-releasing hormone (TRH) from the hypothalamus. Both  $T_3$  and  $T_4$  are capable of exerting negative, or inhibitory, feedback upon the release of TRH and TSH. Refer to Figure 1.<sup>1-5</sup>

Figure 2 illustrates the peripheral metabolic pathways of thyroxine ( $T_4$ ).

## Abnormal secretion of the thyroid hormones

There are two main categories of abnormal thyroid gland functioning, namely hypothyroidism (i.e. insufficient thyroid hormone secretion) and hyperthyroidism (i.e. an excessive secretion of the thyroid hormones).

### Hypothyroidism

Hypothyroidism refers to low plasma levels of the thyroid hormones due to their inadequate production or secretion by the thyroid gland. Inadequate levels of circulating thyroid hormone during foetal development and early infancy will result in a condition known as cretinism, which is characterised by dwarfism

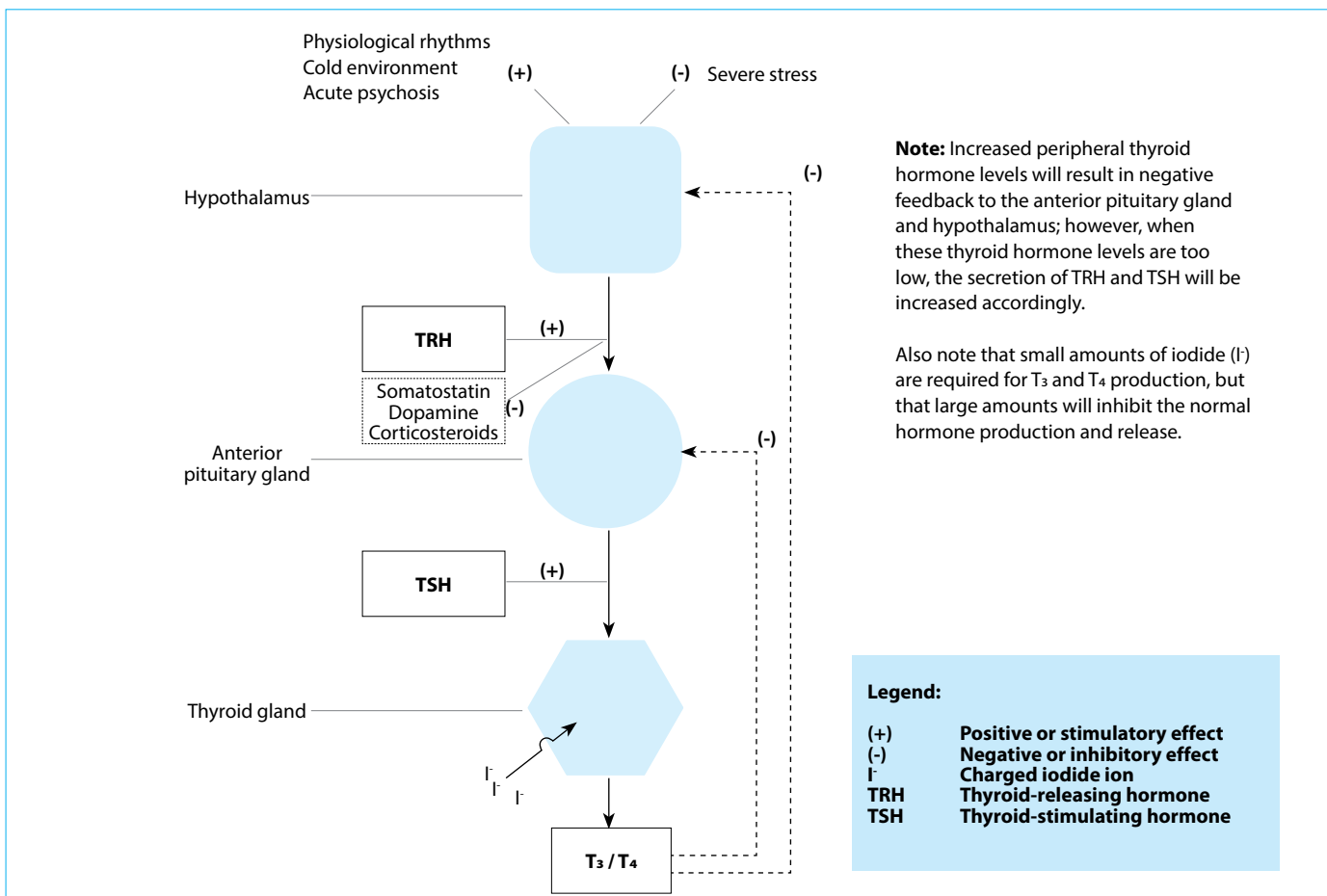


Figure 1: Simplified diagram of the hypothalamic-pituitary-thyroid gland axis<sup>3</sup>

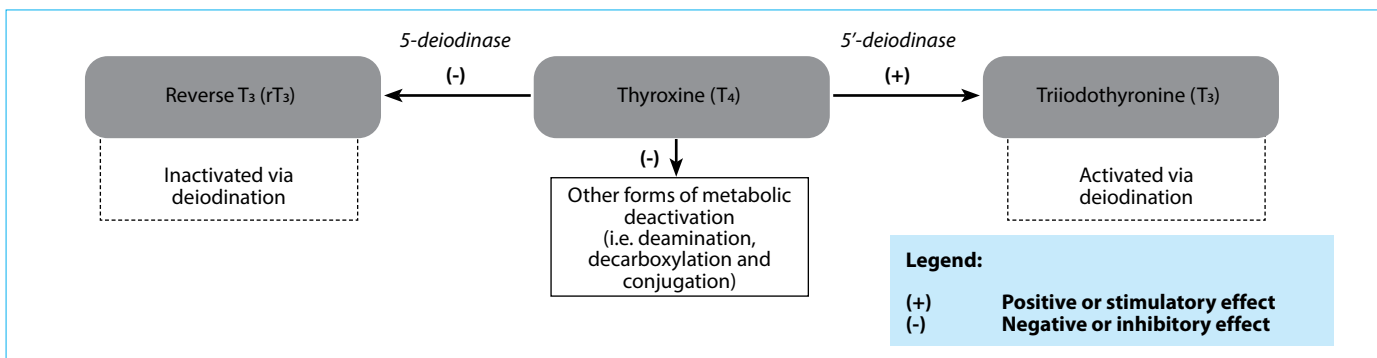


Figure 2: The peripheral metabolism of thyroxine<sup>3</sup>

and irreversible mental retardation. Three underlying mechanisms may result in the hyposecretion of thyroid hormone:<sup>1,3-5</sup>

- Inadequate dietary intake of iodine, which is probably the most common cause of hypothyroidism worldwide
- A secondary insufficiency due to deficient levels of TRH and/or TSH (a few drugs are, amongst other causes, capable of inducing an iatrogenic hypothyroidism.<sup>3</sup> These include the iodides and amiodarone, lithium, the thionamides, ethionamide and aminogluthimide.)
- As a result of primary gland failure of the thyroid itself (or following its surgical removal via thyroidectomy).

Sufficiently severe cases of hypothyroidism produce and are subsequently referred to as myxoedema. Patients with hypothyroidism experience a generalised slowing-down of all their body functions. Goitre, which refers to enlargement of the thyroid gland, may or may not be present in these patients. A wide variety of clinical signs and symptoms may accompany the condition, both physically and mentally (see Figure 3). In children, there may be a marked hindrance of normal growth and development, including mental retardation.<sup>3,4</sup>

In addition, in the case of Hashimoto's disease (also referred to as Hashimoto's thyroiditis, and considered to be a very common cause of hypothyroidism in adults), patients develop hypo-

functioning of the thyroid gland in the presence of antithyroid auto-antibodies. This condition is characterised by lymphocytic infiltration of the gland itself, and a gradual loss of both thyroid tissue and function.<sup>6</sup> The two major thyroid antigens in patients with Hashimoto's disease are thyroglobulin (Tg) and thyroid peroxidase (TPO), with highly-specific IgG-antibodies against these targets that are present in the serum. However, it is believed that these antibodies are of a somewhat lesser importance in the pathogenesis of the disease, with T-cell mediated cytotoxic effects and activated apoptotic pathways playing a more significant role in the destruction of the thyroid gland.<sup>6</sup>

### Hyperthyroidism

The condition is also referred to as thyrotoxicosis, and is the result of excessive, or hypersecretion of thyroid hormone. Hyperthyroidism is most commonly caused by an autoimmune condition known as Graves' disease. The other two causative mechanisms of hyperthyroidism are:

- Thyroid tumours that secrete excessive amounts of thyroid hormone
- A secondary excess due to abnormally high levels of TRH or TSH.<sup>1,5</sup>

In some cases, a subacute thyroiditis (or inflammatory thyroid disease) may also occur.<sup>4</sup>

Common signs and symptoms are highlighted in Figure 3.

Graves' disease is also referred to as toxic goitre. In this autoimmune disorder, antibodies against thyroidal antigens are produced by activated B-lymphocytes. In particular, these antibodies are of the TSH-R Ab [stim] type, meaning that they stimulate the TSH-receptors on the cells of the thyroid gland. In addition, orbital fibrocytes may be stimulated in the same way, ultimately resulting in wide-ranging remodelling of the tissues surrounding the eye. This produces the characteristic protrusion of the eyeballs, referred to as exophthalmos. It follows that the stimulation of thyroidal TSH-receptors will result in an overproduction of thyroid hormones.<sup>3,4</sup>

### Laboratory diagnosis of thyroid disorders

Thyroid function tests may be performed, which will typically include the levels of TSH and free  $T_4$ , as well as  $T_3$ , in the blood-stream. In hypothyroidism, the levels of  $T_3$  and  $T_4$  will be low, with a compensatory increase in the level of TSH. The reverse is found in thyrotoxicosis, where the TSH-level will be decreased, and the free levels of the thyroid hormones conversely increased.<sup>1,5</sup>

The best indicators of adequate thyroid hormone replace therapy, are the TSH and  $T_4$ - serum levels.<sup>7</sup>

### Pharmacology of thyroid and antithyroid drugs

Drug therapy used in the management of thyroid conditions have been utilised for more than a century. Antithyroid drugs (ATDs) are used in the management of hyperthyroidism, whilst drugs used to restore normal thyroid hormone concentrations in body tissue, are used in the management of hypothyroidism (i.e. thyroid hormone replacement therapy). The latter is aimed at providing symptomatic relief, and in newborn infants to prevent neurological deficits (i.e. cretinism), as well as to reverse the biochemical abnormalities associated with hypothyroidism.<sup>3,4,8</sup>

### Non-pharmacological management

Non-pharmacological measures can also be used in the management of hypo- and hyperthyroidism. Hyperthyroidism may either be managed by conservative treatment (i.e. ATDs) or by reduction or ablation of the thyroid tissue (e.g. radioactive iodine, thyroidectomy).<sup>12</sup> In the management of hyperthyroidism, the surgical removal of the hyper-secreting thyroid gland is an option in patients with clinical symptoms, which include:<sup>9</sup>

- Large thyroid (> 80 g)
- Severe ophthalmopathy
- Decreased response to ATDs

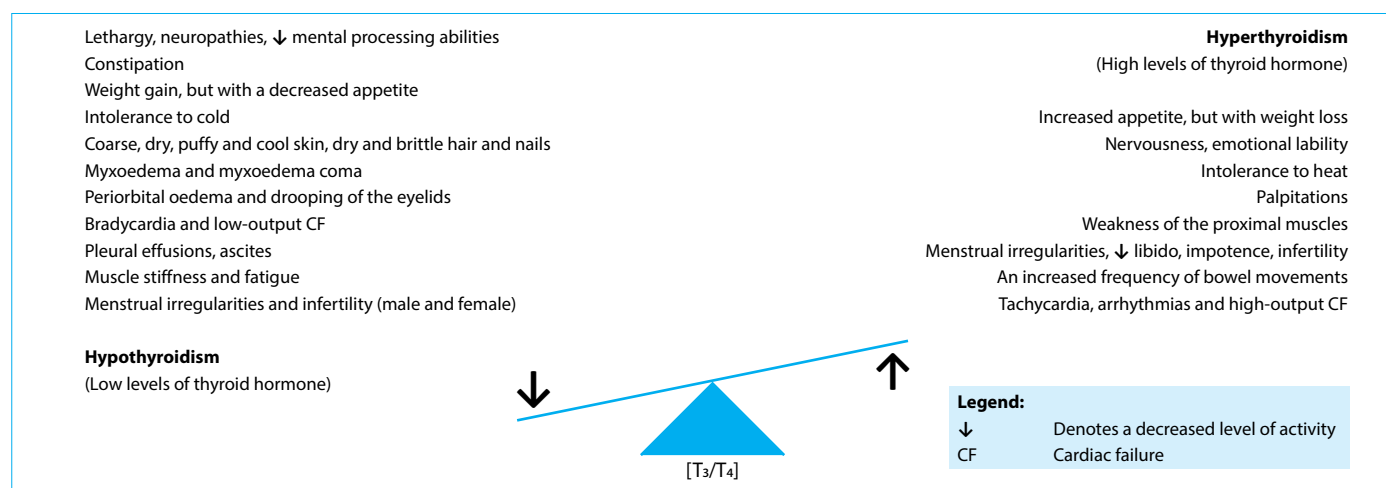


Figure 3: Common signs and symptoms of hypothyroidism versus hyperthyroidism<sup>3,4</sup>

Symptomatic hypothyroidism	Sub-clinical hypothyroidism	Symptomatic hypothyroidism with normal TSH-levels
<ul style="list-style-type: none"> <li>• TSH-level &gt; 10 mU/litre</li> <li>• Treatment with levothyroxine (T<sub>4</sub>), probably for life</li> <li>• Liothyronine (T<sub>3</sub>) may be used when a rapid response is required (it is more potent and has a higher bio-availability, but a shorter t<sub>1/2</sub> when compared to T<sub>4</sub>)</li> </ul>	<ul style="list-style-type: none"> <li>• TSH-level between 5 and 10 mU/litre; free serum thyroxine-level within its reference range</li> <li>• Routine medicine management is controversial</li> <li>• Levels should be confirmed after 3 to 6 months and management re-assessed</li> </ul>	<ul style="list-style-type: none"> <li>• Assess for possible alternative diagnoses</li> <li>• Treat accordingly</li> <li>• Test-dosages of levothyroxine may be initiated to assist in making the diagnosis</li> </ul>

Figure 4: Overview of the management of hypothyroidism<sup>3,4,7,10,13,14</sup>

Following a thyroidectomy, hyperthyroidism may be persistent post-surgery in 0.6 % to 17.9 % of patients suffering from Graves' disease, and especially in children. However, the complications of surgery most frequently include hypothyroidism, and less commonly hypoparathyroidism and vocal cord abnormalities.<sup>8,9</sup>

The management of hypothyroidism will depend on the levels of TSH and the presenting symptoms of the patient. Refer to Figure 4 for an overview of the management of hypothyroidism.<sup>10</sup>

### Hyperthyroidism

Methimazole, carbimazole, and propylthiouracil (PTU) are relatively simple molecules known as thionamides, and contain a sulfhydryl group and a thiourea moiety within a heterocyclic structure; these drugs are also the mainstay of antithyroid-drug therapy.<sup>8,11,12</sup> Collectively they are referred to as the antithyroid drugs (ATDs). Their main mechanism of action is through the blockade of thyroid hormone synthesis by inhibition of thyroid peroxidase. This enzyme catalyses iodide oxidation, iodination of tyrosine residues onto thyroglobulin, and coupling of the iodotyrosines (monoiodotyrosine, MIT, and diiodotyrosine, DIT) to form the thyronines, tetraiodothyronine or thyroxine (T<sub>4</sub>), and triiodothyronine (T<sub>3</sub>). An additional effect of PTU is to inhibit monodeiodination of thyroxine to triiodothyronine.<sup>8,11,12</sup> They also have immunosuppressive actions, which are useful in the management and treatment of Graves' disease.

Antithyroid drugs are used in two ways:<sup>8</sup>

- As the primary treatment for hyperthyroidism
- Used in preoperative preparation before radiotherapy or surgery.

The following conditions may be managed with ATDs: Graves' disease, toxic adenoma, and toxic multinodular goitre. In the case of toxic adenoma and toxic multinodular goitre, ATDs are used as a tool to prepare the patient for more definitive treatment. ATDs are used as the primary treatment option in pregnant patients, as well as in children and adolescents.<sup>11,12</sup> It is recommended for the administration of methimazole, specifically during pregnancy, to avoid liver failure associated with propylthiouracil.<sup>14</sup>

When prescribed for Graves' hyperthyroidism, these drugs are used to induce a remission, which is defined as having normal

thyroid hormone levels for one year after drug treatment has been stopped.<sup>11,12</sup>

In the management of hyperthyroidism, and when patients are fully compliant with the medicines prescribed, the ATDs may be highly effective. The choice of drug to be used is based on a decision made between the prescriber and the patient. However, methimazole has the advantage of a once-daily dosing regimen and serum thyroxine and triiodothyronine levels decrease more rapidly in patients treated with this drug. The risk of agranulocytosis is also lower with methimazole, and when used in moderate dosages may improve compliance and makes this drug preferable to propylthiouracil.<sup>8,11</sup>

Once a patient has been started on treatment of ATDs, follow-up testing of thyroid function should be undertaken every four to six weeks, until the thyroid function is stable or until the patient is diagnosed as being euthyroid (i.e. having normal thyroid function). Clinically most patients improve considerably after four to twelve weeks; drug dosing can be reduced to maintain normal thyroid function. Administering the incorrect dosage, or not monitoring the dosage, can produce hypothyroidism or even goitre. Treatment with ATDs will normally last for 12 to 18 months.<sup>8</sup>

The term, thyroid storm, refers to a rare, potentially life-threatening, overexaggerated expression of hyperthyroidism, during which the patient may develop the following clinical manifestations:

- Severe agitation and a state of mental confusion
- Hyperthermia
- Overt tachycardia, which may be accompanied by acute cardiac failure
- Loss of consciousness.

Drugs that are typically used in the management of such an episode, include carbimazole, Lugol's solution, propranolol and a suitable glucocorticosteroid. In addition, the patient should be admitted to an intensive care unit and general supportive measures will need to be instituted.<sup>7</sup>

### Side-effects experienced with ATDs

ATDs are associated with side-effects that may range from being minor, to being potentially life-threatening or even lethal. Methimazole has dose-related side-effects, whereas

propylthiouracil side-effects seem to be less associated with the actual dosage. The milder side-effects are usually self-limiting and are observed in less than 5% of cases; these side-effects seem to be noticed during the initial phases of treatment when the daily dosage administered is higher than usual.<sup>11,12</sup>

When more severe side-effects are experienced with one agent, another thionamide can serve as a substitute; however, cross-sensitivity has been described in as much as 50% of patient cases.<sup>8,11,12</sup> Side-effects should be evaluated and if serious the drug should be discontinued. Side-effects of the ATDs are listed in Table I and have been provided in the form of a checklist, which may be utilised by the pharmacist in the practice setting.<sup>11,12</sup>

### $\beta$ -adrenergic blockers

$\beta$ -adrenergic blockers are used in symptomatic management of hyperthyroidism due to Graves' disease or toxic nodules awaiting surgery. They are used to reduce the sympathomimetic symptoms induced by hyperthyroidism, such as palpitations, anxiety and tremors, and should be discontinued once the patient becomes euthyroid. All  $\beta$ -blockers may be used in the management of hyperthyroidism; atenolol and nadolol may improve compliance as they only necessitate a once-daily dosing routine. Propranolol may be used in the acute management of thyroid storm.  $\beta$ -blockers should still be used with caution in patients with asthma and heart failure as co-morbid conditions.<sup>7,11</sup>

### Radioactive iodine (RAI)

Recurrent hyperthyroidism and Graves' disease may be treated with radioactive iodine. RAI is used as the  $\beta$ - particles emitted causes destruction of thyroid tissue with the end-goal of achieving a patient with either euthyroid or hypothyroid levels. Sodium iodide 131 (<sup>131</sup>I) is the RAI of choice in the treatment of Graves' disease and toxic autonomous nodules. RAI is a colourless and tasteless liquid. Dosing regimens and the contact-time following the administration of RAI is not well established; however, low dosages may be more convenient for the patient.<sup>11,12</sup>

### Iodides

Iodine is a temporary solution that inhibits the release of thyroid hormones for only a few days or weeks (one to two weeks), and for this reason its usefulness is limited to the preparation of patients with Graves' disease for surgery, as well as to treat patients suffering from a thyrotoxic crisis (thyroid storm). The recommended daily adult iodide intake is 150 mcg, up to 250 mcg for children and 200 mcg during pregnancy and lactation. However, chronic use of iodides in pregnancy should be avoided and fetal goitres might result.<sup>3</sup> The inhibitory effect is achieved via the blocking of hormone release, by interfering with hormone biosynthesis through competing with intrathyroidal iodide use. This decreases the size and vascularity of the thyroid gland. Preparations are

**Table I:** Side-effects of the antithyroid drugs<sup>3,4,11,12,14</sup>

Body system	Side-effect	Frequency (and drug involved)	Experienced by the patient (✓ or ✗)
<b>Blood</b>	Mild leukopenia	Relatively frequent	
	Agranulocytosis	Uncommon	
	Aplastic Anaemia	Very rare	
	Thrombocytopenia	Very rare	
	Pancytopenia	Very rare	
<b>Skin</b>	Skin rash	Very common	
	Urticaria	Very common	
	Itching	Very common	
	Generalised rash	Very rare	
	Alopecia	Very rare	
<b>Hepatic (liver)</b>	Hepatocellular necrosis	Rare (PTU)	
	Cholestasis	Very rare (MMI)	
<b>Collagen</b>	Arthralgia	Common	
	SLE-like syndrome	Very rare (PTU>MMI)	
	Vasculitits	Very rare (PTU)	
<b>Embryopathy</b>	Choanal atresia, oesophageal atresia, cardiac defects, aplasia cutis	Very rare (MMI)	
	<i>Situs inversus</i> $\pm$ dextrocardia, unilateral kidney a/dysgenesis, cardiac outflow tract defect	Very rare (PTU, uncertain)	
<b>Miscellaneous</b>	Loss of taste	Rare (MMI)	
	Hypothrombinaemia	Rare (PTU)	
	Insulin auto-antibodies	Very rare	

[MMI = methimazole; PTU = propylthiouracil; SLE = Systemic Lupus Erythematosus]

available as either a saturated potassium iodide solution (SSKI) or as a Lugol's solution.<sup>11,12</sup>

### Hypothyroidism

When hypothyroidism is left untreated it can result in cardiac failure, psychosis, and coma.<sup>13</sup> Thyroxine-replacement therapy is highly effective and has been used in its rudimentary form since 1891.<sup>13</sup> Correcting myxedema in elderly patients with underlying coronary artery disease should be done with caution as the low levels of thyroid hormone could be providing protection to the heart against, e.g., myocardial infarction. Since the development of the fetal brain depends on maternal thyroxine, a 25-30% increase in thyroxine dose may be necessary in pregnant, hypothyroid patients.<sup>3</sup> The major indications for thyroid-replacement therapy remains:<sup>14</sup>

- Hypothyroidism
- Cretinism
- TSH suppression therapy in patients suffering from thyroid cancer.

Sherwood noted that replacement thyroid hormone pills are used to treat hypothyroidism, except when it is caused by an iodine deficiency, in that case, dietary iodine is prescribed. Levothyroxine (T<sub>4</sub>; L-thyroxine) is a synthetic thyroid hormone and remains the drug of choice for thyroid-replacement therapy as it is chemically stable, not expensive, and with uniform potency.<sup>15</sup> Dosages of levothyroxine (LT<sub>4</sub>) can be related to bodyweight (dosed at 1.8 µg per kg in adults, 0.5 µg per kg in older adults) and is dosed at higher levels in infants (10-15 mcg/kg/day) and young children.<sup>10,14</sup> When therapy is initiated it should be at the lower end of the calculated dose; i.e. for a 70 kg adult, 125 µg per day.<sup>10</sup> To initiate therapy at 25-50 µg per day and titrating upwards is unnecessary and prolongs the desired response to treatment.<sup>10,15</sup> Dosages should be titrated using serum thyrotropin concentrations and should be undertaken four to six weeks after a new thyroxine dosage has been prescribed. Thereafter, this should be done annually, or whenever a patient presents with persistent symptoms of either hypo- or hyperthyroidism.<sup>1,10,14</sup>

The target level of treatment is determined by the following:<sup>10</sup>

- The patient expressing a sense of well-being, with signs and symptoms decreasing in frequency and severity
- TSH-levels at the lower end of the reference range (0.4 to 2.5 mU/litre).

It is important to avoid a fully-suppressed TSH (< 0.1 mU/litre); each patient should be assessed using TSH-levels and symptoms, and dosed individually.<sup>10</sup> Patient counselling when initiating the therapy should include the advice as listed in Table II.

### Side-effects experienced with levothyroxine therapy

Side-effects experienced to thyroid-replacement therapy are related to excessive thyroid hormone action and may include the following:<sup>5,10,12</sup>

- Symptomatic thyrotoxicosis
- Subclinical thyrotoxicosis (with an increase in bone loss)
- Atrial tachyarrhythmias
- Heart failure
- Angina pectoris
- Myocardial infarction.

Patients who were previously diagnosed with underlying ischaemic heart disease may exacerbate myocardial ischemia once euthyroidism has been established:<sup>10,12</sup> Synthetic products very rarely produce allergic or idiosyncratic reactions, as were previously experienced with the natural or animal-derived products.<sup>5</sup>

Hyperthyroidism may lead to a decrease in bone density due to hyper-remodelling of the cortical and trabecular bone, which could result in an increased likelihood of bone fractures.<sup>5</sup> Acute sympathomimetic symptoms and hair loss have also been experienced after thyroxine treatment has been initiated.<sup>13</sup>

### Conclusion

The thyroid gland plays a vital role in the maintenance of a normal basal metabolism in the human body. Abnormalities in thyroid

**Table II:** Patient advice when initiating levothyroxine therapy<sup>10</sup>

Patient advice	Experienced by the patient (✓ or ✗)
It may take a week or more for you to start feeling better. Levothyroxine has a half-life of seven days.	
If you miss one dose, the effect might not be noticeable (due to the long half-life), take as soon as you remember.	
Other symptoms (e.g. muscle stiffness/weakness and mental effects may take several months to resolve once the chemical imbalance has been corrected).	
Levothyroxine should be taken on an empty stomach, as it will maximise absorption.	
Treatment will be life-long, and dose adjustments will only be made according to hormone (thyroid) levels. Hormone levels should be taken once a year.	
The following drugs should be avoided or taken with caution when taking levothyroxine therapy:	
Drugs that will <b>prevent absorption</b> of levothyroxine (e.g. calcium salts, ferrous sulphate, aluminium hydroxide, cholestyramine).	
Drugs that <b>increase the clearance</b> of levothyroxine, in other words drugs that will cause a decrease in levothyroxine levels (e.g. phenytoin, carbamazepine, phenobarbitone and rifampicin).	

hormone levels could, therefore, have far-reaching effects on various body systems, organs and tissues. Such abnormalities typically fall into one of two categories, namely hypo- or hyperthyroidism, and require effective treatment to either replace the deficient levels of thyroxine in the bloodstream, or to antagonise the excessive levels of circulating thyroid hormone. Patients who are using such therapies in the long-term will require additional monitoring and support by the multidisciplinary team, including the pharmacist.

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