

## **Functional thyroid disorders in the pharmacy setting – how can we help our patients?**

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### **Abstract**

Functional thyroid disorders (hypothyroidism and hyperthyroidism) are amongst the most common endocrine disorders pharmacists encounter on a daily basis. They are highly prevalent in iodine-replete areas, and affect women about 10 times more often than man. Hypothyroidism (thyroid hormone deficiency) is usually caused by Hashimoto's thyroiditis, an autoimmune disorder that leads to gradual thyroid destruction. The drug-of-choice for treating hypothyroidism is levothyroxine, a synthetic form of thyroxine. Key points which need to be discussed with patients who are prescribed levothyroxine for the first time are when/how to administer this drug, how its effects are monitored, what drugs may affect its efficacy, and the importance of properly treating hypothyroidism during pregnancy. Hyperthyroidism (increased production of thyroid hormones) is most often caused by Graves' disease, another thyroid autoimmune disorder in which stimulatory autoantibodies against the TSH receptor lead to increased thyroid function. Graves' disease is most commonly treated with thionamide drugs (thiamazole, carbimazole or propylthiouracil) and patients using these drugs should be advised on the monitoring requirements, duration of treatment, and how to recognize possible serious adverse effects (agranulocytosis and hepatotoxicity), and informed that these drugs must be used during pregnancy in order to reduce the risk of adverse outcomes for the mother and baby.

**Key words:** hypothyroidism, hyperthyroidism, levothyroxine, thionamide drugs

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## **Introduction**

Disorders of the thyroid gland are one of the most prevalent diseases affecting modern society, and they are especially common in female patients (1). Among the many possible thyroid diseases, functional disorders, i.e., hypothyroidism (thyroid hormone deficiency) and hyperthyroidism (overactivity of the thyroid gland with increased production of thyroid hormones), are the ones most likely to be encountered by pharmacists on a daily basis, seeing as they are usually pharmacologically treated (2, 3).

The following article provides practical suggestions (organized in the form of simple clinical questions) on how to counsel patients with functional disorders of the thyroid gland on matters such as the appropriate use of prescribed medications, monitoring requirements, how to manage adverse effects and when to stop treatment. It also provides information on the most clinically significant interactions with other medicines, food and dietary supplements. Additionally, two infographics with the most frequently asked questions regarding treatment of hypothyroidism and hyperthyroidism have been included to aid patients starting drug therapy for their thyroid disorder (Figures 1 and 2).

## **Hypothyroidism**

Hypothyroidism is a prevalent medical condition characterized by thyroid hormone deficiency. The most common form is primary hypothyroidism, in which reduced production of thyroid hormones is the result of a disorder or destruction of the thyroid gland. Biochemically, primary hypothyroidism is characterized by increased levels of thyroid-stimulating hormone (TSH). Depending on the levels of free thyroxine (FT<sub>4</sub>), hypothyroidism can be classified as clinical (overt; reduced FT<sub>4</sub> levels) or subclinical (normal FT<sub>4</sub> levels) (2, 4).

Given that most organ systems in the body are sensitive to the effects of thyroid hormones, the possible symptoms and signs of hypothyroidism are numerous (2, 4, 5). Some of the more common clinical manifestations of this condition are listed in Table I. Of particular note is the effect of hypothyroidism on the child-bearing potential of young women. Uncontrolled hypothyroidism is associated with reduced fertility, as well as an increased risk of several obstetric complication (see question 13 for further information) (2, 6). In addition, certain signs and symptoms of overt hypothyroidism overlap with those of psychiatric disorders (such as depression), and in these cases it can be challenging to determine if the thyroid disorder is the cause of psychiatric symptoms or if patients have an underlying psychiatric disease (2).

**Table I** Clinical manifestations of functional thyroid disorders (2-5, 12, 13)**Tabela I** Kliničke manifestacije funkcionalnih tiroidnih poremećaja (2-5, 12, 13)

<b>Organ system</b>	<b>Hypothyroidism</b>	<b>Thyrotoxicosis/ hyperthyroidism</b>
<b>General</b>	Fatigue and tiredness Cold intolerance	Fatigue Heat intolerance
<b>Thyroid</b>	Goiter in Hashimoto's thyroiditis	Goiter in Graves' disease
<b>Skin</b>	Dry coarse skin Hair loss Brittle nails Puffy face (periorbital region), swelling of the hands and feet (myxedema)	Warm moist skin Hair loss
<b>Gastrointestinal</b>	Constipation	Diarrhea
<b>Reproductive</b>	Menorrhagia Oligomenorrhea and amenorrhea Subfertility	Oligomenorrhea Lowered libido Gynecomastia
<b>Cardiovascular</b>	Bradycardia Diastolic hypertension	Palpitations Tachycardia Atrial fibrillation (elderly)
<b>Neurologic/ psychological</b>	Poor memory Difficulty concentrating Slow speech Depression	Hyperactivity Irritability and dysphoria Insomnia Tremor Muscle weakness and proximal myopathy
<b>Metabolic</b>	Weight gain (with poor appetite)	Weight loss (with increased appetite)
<b>Ocular</b>	Rarely, orbitopathy may develop in patients with Hashimoto's thyroiditis	Lid retraction possible in all forms of thyrotoxicosis Graves' disease can be associated with specific ocular symptoms (Graves' orbitopathy)

It is estimated that the prevalence of spontaneous clinical hypothyroidism in adults is around 1-2%. The disorder is more common in older people and about 10 times more common in women than in men. The prevalence of subclinical hypothyroidism is even higher and is around 4-9% in iodine-replete areas (1). Usually, primary hypothyroidism is caused by Hashimoto's thyroiditis, an autoimmune disorder that leads to the slow destruction of the thyroid gland and gradual development of signs and symptoms. Patients with Hashimoto's thyroiditis have serological signs of thyroid autoimmunity, such as elevated levels of anti-thyroperoxidase antibodies and anti-thyroglobulin antibodies. Additionally, primary hypothyroidism can also develop because of iatrogenic causes (i.e. surgical removal or destruction of the thyroid gland with radioactive iodine in the

treatment of hyperthyroidism or thyroid cancers), or the use of certain medications (such as amiodarone, lithium, interferon  $\alpha$ , protein kinase inhibitors, etc.) (2, 4, 5).

A specific, though not common, form of hypothyroidism is congenital hypothyroidism, i.e. thyroid hormone deficiency present upon birth. Although rare, congenital hypothyroidism has detrimental effects on the physical and neurocognitive development of newborns and should be promptly treated (certain specific points of treating congenital hypothyroidism are highlighted in the text below) (2, 4, 5).

Even though hypothyroidism is highly prevalent among adult patients, non-selective routine screening for this disorder is not recommended for the general adult population. However, certain patient populations are at a higher risk of developing thyroid dysfunction and targeted screening for thyroid disorders can be considered to be of benefit. These include: patients with goiter, previous exposure to radioactive iodine, history of neck irradiation, use of medication with thyroid disrupting properties, patients with other autoimmune disorders (such as type 1 diabetes) and women of child-bearing potential (with symptoms of thyroid dysfunction, personal or family history of thyroid disorders, personal history of infertility or miscarriage). Unlike adult hypothyroidism, routine screening for congenital hypothyroidism in newborns is highly beneficial (seeing as congenital hypothyroidism is the main preventable cause of intellectual impairment) and is employed in most countries (2).

#### *1. How should patients with clinical hypothyroidism be treated?*

The standard of care for the treatment of hypothyroidism is levothyroxine supplementation therapy. Levothyroxine is a synthetic form of T<sub>4</sub> and has several favorable characteristics making it the drug of choice for hypothyroidism treatment: low cost, excellent safety profile, good intestinal absorption and long duration of effects (enabling once-daily dosing). Synthetic forms of triiodothyronine (T<sub>3</sub>; liothyronine) are also available; however, they are not routinely used in the treatment of hypothyroidism (because of the higher price, shorter duration of effects, higher frequency of cardiovascular adverse effects, and difficult monitoring of therapy) (4).

#### *2. How can levothyroxine supplementation therapy be started?*

Supplementation therapy can be started in one of two ways:

- a) **Full replacement dose:** Patients are prescribed an initial dose based on their body weight (usually 1.6 micrograms/kg of body weight). This approach is commonly used in younger and middle-aged patients without significant cardiovascular comorbidities. It is also adequate in cases of markedly increased levels of TSH (4).
- b) **Partial replacement with gradual dose titration:** Patients are prescribed a low initial dose (12.5-25 micrograms daily) and the dose is gradually increased according to the achieved TSH levels. This approach is appropriate for older patients and for patients with serious cardiovascular comorbidities (especially ischemic heart disease) because of the cardiovascular effects of thyroid hormones. This approach is also

adequate for patients with milder forms of hypothyroidism (slightly increased levels of TSH) (4).

### 3. What factors affect levothyroxine requirements?

The required dose of levothyroxine depends on several factors, such as body weight, etiology of hypothyroidism, age, degree of TSH elevation, pregnancy status and comorbidities. How these factors affect levothyroxine dosing is presented in Table II.

**Table II** Most significant factors affecting levothyroxine dosage requirements in the treatment of hypothyroidism (2, 4, 5, 11)

**Tabela II** Najznačajniji faktori koji utiču na doziranje levotiroksina u terapiji hipotiroidizma (2, 4, 5, 11)

<b>Age</b>	Thyroid hormone requirements are greatest in the early life period and decrease with aging (e.g. in newborns with congenital hypothyroidism the required dose of levothyroxine is 10 micrograms/kg/day, whereas the typical adult dose is 1.6 micrograms/kg/day)
<b>Etiology of hypothyroidism</b>	Larger doses of levothyroxine are usually required for patients with hypothyroidism following total thyroidectomy (removal of the thyroid gland) than for those with Hashimoto's thyroiditis or after radioactive iodine administration (these patients may have residual functional thyroid tissue).
<b>Severity of hypothyroidism</b>	Lower doses of levothyroxine are needed for subclinical compared to clinical hypothyroidism. Larger TSH values require higher doses of levothyroxine for normalization.
<b>Comorbidities</b>	In patients with cardiovascular diseases, particularly ischemic heart disease, gradual dose titration is recommended, because of the positive inotropic and chronotropic effects of levothyroxine.  Certain gastrointestinal disorders are associated with lower levothyroxine absorption (e.g. <i>Helicobacter pylori</i> gastritis, atrophic gastritis, coeliac disease). These patients may require higher levothyroxine doses (until their gastrointestinal disease is adequately managed).
<b>Pregnancy status</b>	The dosage of levothyroxine usually needs to be increased during pregnancy. Additional note: TSH reference ranges are different during pregnancy compared to non-pregnant patients.

### 4. How should levothyroxine be administered?

Levothyroxine is taken orally. To ensure optimal absorption, it is best to administer levothyroxine in the morning, 60 min before breakfast, with a glass of plain water (other beverages, such as coffee, have been found to impair levothyroxine absorption to a variable degree, so it is best to avoid them) (4, 7). Alternatively, levothyroxine may be administered 30 min before breakfast or at bedtime (2-3 hours following the last meal); however, these schedules are associated with lower bioavailability (4). The timing should

be selected according to the needs of individual patients in order to promote adherence, e.g. some patients cannot wait 60 min before eating or may need to take other medications in the morning which also require a prolonged period of fasting (e.g. bisphosphonates). In extreme cases, when adequate daily adherence to supplementation therapy cannot be achieved, clinicians may opt to administer a full week's dose of levothyroxine once weekly (4).

*5. Are there any medications/supplements that can affect levothyroxine efficacy?*

Levothyroxine absorption can be substantially reduced in cases of concomitant use with iron preparations, calcium preparations and antacids. To reduce the risk of this interaction, it is best to administer them 4 hours after levothyroxine (4, 7). Concomitant use of these preparations with levothyroxine is likely to occur in everyday practice, seeing as hypothyroid patients are usually women who use iron and calcium supplements for the treatment/prevention of anemia or osteoporosis, respectively.

Proton pump inhibitors also may reduce the absorption of levothyroxine (by increasing gastric pH values), and consequently reduce the efficacy of supplementation therapy (manifested by increases in TSH levels) (4, 7, 8). Patients requiring prolonged treatment with proton pump inhibitors (e.g. due to gastroesophageal reflux disease) could potentially require an increase in their levothyroxine dosage.

The use of estrogen hormones (e.g. in the form of hormonal contraception or hormone therapy for menopausal symptoms) can also increase levothyroxine requirements by increasing the levels of thyroxine-binding globulin, the main transport protein for thyroid hormones in the blood. Enzyme inducers (e.g. carbamazepine, phenytoin, rifampicin) are also known to increase levothyroxine requirements by promoting its metabolic breakdown (4).

Certain soy-based products are associated with the reduction of levothyroxine absorption. This could be of practical significance for treating congenital hypothyroidism in infants and nursing children, as levothyroxine tablets are usually crushed and administered with formula. In these cases, non-soy based formulas should be used to administer levothyroxine, or it should be administered with breastmilk or water (4, 7).

*6. Can levothyroxine affect the efficacy of other medicines?*

Levothyroxine can increase the effects of coumarin anticoagulant drugs (warfarin), and anticoagulant dosage reduction may be needed to avoid excessive anticoagulation and potential bleeding. Additionally, levothyroxine therapy may increase blood glucose levels, and in diabetic patients dosage adjustments of antidiabetic drugs may be needed (9).

*7. How should levothyroxine therapy be monitored?*

The success of levothyroxine supplementation is assessed by measuring the levels of TSH and FT<sub>4</sub> every 4-6 weeks until normalization of hormone levels. If TSH levels are above the upper limit of the reference range, the dose should be increased (usually by 25

micrograms), and *vice versa* – if TSH levels are below the lower limit, the dosage should be decreased (4).

When euthyroidism is achieved, therapy can be monitored by measuring TSH levels every 6-12 months. The reference range for TSH is 0.4-4 mIU/L; slight deviations from this reference range are possible depending on the laboratory and the specific method used to measure TSH levels. Additionally, in older patients (over 80 years of age) higher TSH levels (4-7 mIU/L) are acceptable, seeing as the level of TSH physiologically increases with aging (4, 10).

There are no specific requirements for patients to prepare for TSH level measurements, apart from the standard 8-12 h fasting period, i.e. patients can administer their morning dose of levothyroxine before the measurement of TSH levels (TSH is usually not affected by acute levothyroxine administration). However, levothyroxine administration immediately before blood collection can lead to high FT<sub>4</sub> levels (so this should be taken into account when interpreting laboratory results) (11).

*8. How should patients act if they forget to administer their daily dose of levothyroxine?*

If patients miss their daily levothyroxine dose, they can take it as soon as they remember (with appropriate timing with respect to other medicines and meals). However, if it is almost time for them to administer their next dose, the dose should not be doubled and they should omit their missed levothyroxine tablet (9). Another option is to take two daily doses with a 12 h interval between them on the next day (4).

*9. How long should levothyroxine supplementation therapy last?*

In most cases of primary hypothyroidism, levothyroxine needs lifelong administration, such as in the case of hypothyroidism caused by Hashimoto's thyroiditis or by the removal of the thyroid gland (with surgery or radioactive iodine). Shorter therapy is used in cases of transient hypothyroidism caused by other forms of thyroiditis (4, 5).

*10. Should patients always use the same levothyroxine preparation?*

Whenever possible, patients should be kept on the same specific levothyroxine preparation, because switching to a product from a different manufacturer can potentially lead to changes in TSH levels. Consistency with respect to the used levothyroxine product is especially important in certain patient populations where precise titration of levothyroxine is necessary, such as frail patients, pregnant women, thyroid cancer patients, and children with hypothyroidism. However, if a change in product cannot be avoided, patients should be instructed to measure their TSH levels 4-6 weeks after the switch has been made (4). Re-checking TSH levels should also be considered in cases where the used levothyroxine product is reformulated by the manufacturer.

*11. What are the adverse effects of levothyroxine and how to reduce the risk of toxicity?*

Supplementation therapy with levothyroxine is virtually devoid of adverse effects if the dose is adjusted to the patient's individual requirements. In cases of over-substitution (iatrogenic thyrotoxicosis), levothyroxine may lead to the development of atrial fibrillation and osteoporosis. The elderly and women are especially prone to these adverse events and over-supplementation (with low TSH values) should especially be avoided in these populations (2, 4).

*12. Should levothyroxine be used in patients with subclinical hypothyroidism?*

Subclinical hypothyroidism is a mild form of hypothyroidism characterized by elevated TSH levels and normal levels of thyroid hormones. Patients with subclinical hypothyroidism are usually asymptomatic; however, a proportion of them may complain of typical hypothyroid symptoms such as dry skin, memory problems, fatigue, feeling cold, constipation, puffier eyes or muscle cramps. In addition, these patients are at risk for developing clinical hypothyroidism, especially if thyroid antibodies (anti-thyroid peroxidase or anti-thyroglobulin antibodies) are present (2, 10).

When elevated TSH levels are detected, it is generally recommended to re-check their levels after 2-3 months. If the TSH levels are persistently elevated, treatment with levothyroxine may be started (usually in lower doses than those used for clinical hypothyroidism). Treatment is usually advised in younger patients (less than 70 years of age) with TSH levels >10 mIU/L (10). The exceptions are female patients who are planning to become pregnant (see question 13 for further information).

*13. How should hypothyroidism be managed in women planning pregnancy and during pregnancy?*

Hypothyroidism has negative effects on fertility, as well as pregnancy outcomes (e.g. hypothyroidism is associated with higher rates of miscarriages and stillbirths, preterm delivery, low birthweight and has a negative impact on the neurocognitive development of infants). For these reasons, all forms of hypothyroidism (both clinical and subclinical) should be corrected with levothyroxine therapy before conception. In general, it is recommended that TSH levels should be below 2.5 mIU/L before conception. It should also be noted that the TSH reference ranges during pregnancy are different from those for non-pregnant adults. The TSH reference range is 0.1-2.5 mIU/L for the first trimester, 0.2-3.0 mIU/L for the second trimester and 0.3-3.0 mIU/L for the third trimester. TSH levels should be monitored every 4-6 weeks during the first and second trimesters in hypothyroid women (2, 4, 6).

Hypothyroid female patients who were taking levothyroxine before conception usually require an increase in the dose when they become pregnant (30% increase or more). The dose of levothyroxine can also be increased during pregnancy planning (4).



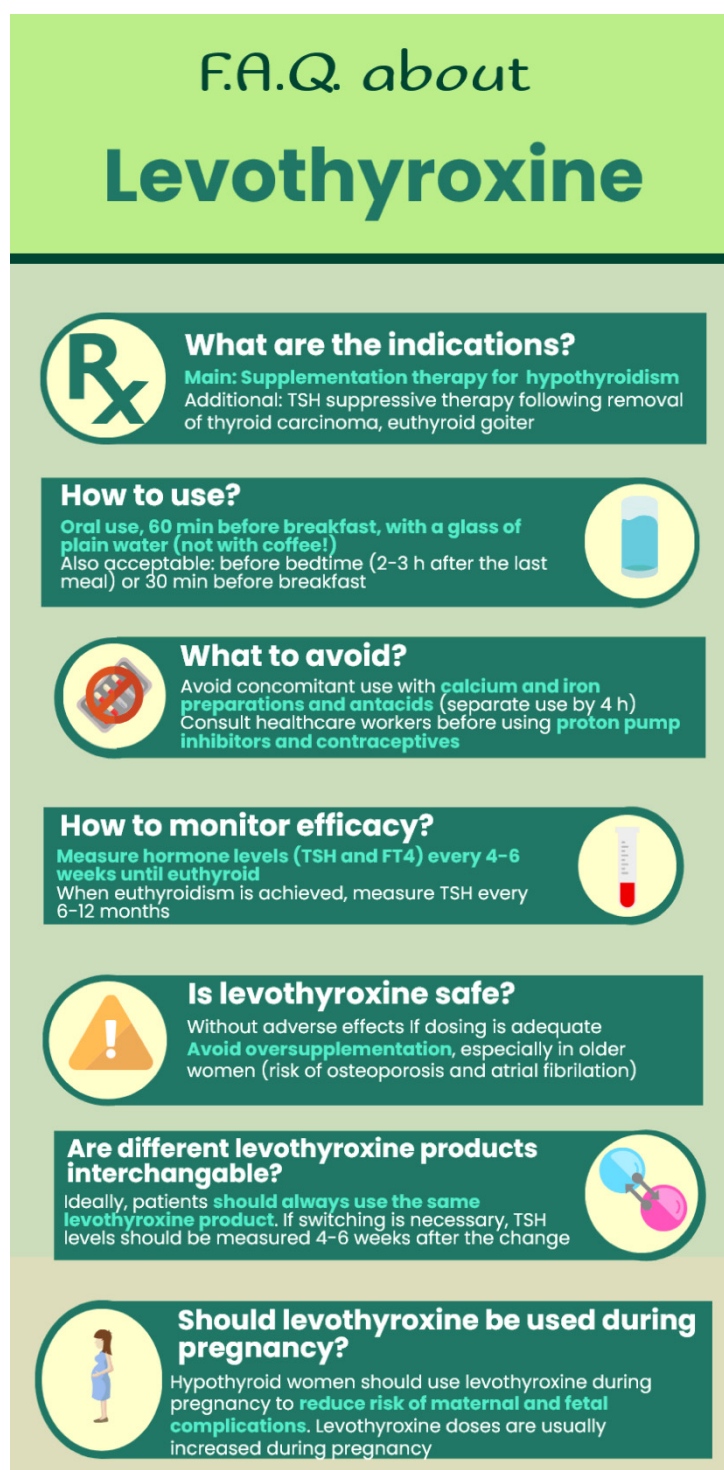


Figure 1. Infographic with frequently asked questions (F.A.Q.) regarding levothyroxine therapy (4)

Slika 1. Infografika sa najčešće postavljenim pitanjima u vezi primene levotiroksina (4)

*14. Do iodine supplements have a role in the treatment of hypothyroidism?*

Iodine supplementation is generally not recommended for the treatment of hypothyroidism, apart from situations where it is caused by iodine deficiency (which is not prevalent in most developed countries). Furthermore, pharmacologic doses of iodine can have a detrimental effects on thyroid function and health and iodine preparation (Lugol's solution of solutions of potassium-iodide) should not be routinely used unless recommended by a healthcare practitioner (2, 4).

*15. When should hypothyroid patients be referred to a doctor?*

As stated earlier (question 11), levothyroxine therapy is usually devoid of adverse effects if the dosage is adequate for the individual patient. However, symptoms such as fatigue, palpitations and chest pain could potentially be due to levothyroxine over-supplementation and patients should be instructed to seek medical help from their doctors. Moreover, patients should be referred to their doctor in cases of persistent symptoms of hypothyroidism, which may indicate that an increase in levothyroxine dosage is necessary.

### **Thyrotoxicosis and hyperthyroidism**

Thyrotoxicosis is a state of elevated blood thyroid hormone levels. The clinical signs and symptoms of thyrotoxicosis are numerous (some of the more important manifestations of this disorder are presented in Table I). The most common cause of thyrotoxicosis is primary hyperthyroidism, i.e. hyperfunction of the thyroid gland with increased production of thyroid hormones. This form of hyperthyroidism is biochemically characterized by low TSH levels and, depending on the levels of FT<sub>4</sub>, can be further classified as clinical (increased FT<sub>4</sub>) or subclinical (FT<sub>4</sub> levels within the reference range). As in the case of hypothyroidism, hyperthyroidism is about 10 times more common in women than in men, and the prevalence is between 0.5% and 2% (1, 3, 12, 13).

Hyperthyroidism is usually the result of Graves' disease (GD), an autoimmune disorder in which stimulatory autoantibodies targeting the TSH receptor imitate the effects of TSH. This leads to an increase in size of the thyroid gland (goiter) and increased production of thyroid hormones (thyrotoxicosis). Subsets of patients with GD develop specific ocular manifestations (Graves' orbitopathy) and sometimes skin changes (pretibial myxedema). GD usually develops in adults between the ages of 20 and 50. However, it can also develop in children (and there are certain specific points to be considered when treating children). Apart from GD, the second most common cause of hyperthyroidism is toxic multinodular goiter (which is more commonly seen in the elderly) (3, 12-14).

*1. How can GD be treated?*

There are three approaches to the treatment of GD – the use of antithyroid drugs (thionamides), radioactive iodine (RAI) and surgical removal of the thyroid gland (thyroidectomy). All three approaches are considered to be valid initial treatment options,

and the choice of treatment modality depends on individual patient characteristics. In most cases, especially in mild to moderate GD and younger patients, antithyroid drugs are initially used for treatment (3, 12-14). The use of thionamide drugs is the only treatment option not associated with a risk of permanent hypothyroidism, whereas RAI and surgical removal of the entire thyroid gland lead to development of hypothyroidism (which requires starting levothyroxine supplementation). However, thionamide therapy has the highest chance of GD relapse (see question 5) (12-14).

2. *Which thionamide drug should be used for GD treatment?*

There are currently 3 available thionamide drugs for GD: thiamazole (also named methimazole), carbimazole (prodrug of thiamazole) and propylthiouracil. All 3 drugs have comparable efficacy in the treatment of GD (12-14).

Today, thiamazole and carbimazole are most commonly used for GD treatment, whereas propylthiouracil is reserved for specific clinical situations (most notably, treatment of GD during the first trimester of pregnancy). This is because thiamazole and carbimazole have a more favorable safety profile and longer duration of effects compared to propylthiouracil - they can be used once daily, whereas propylthiouracil is usually administered 2-4 times daily in the initial phases of GD treatment (12-14).

In the initial phases of treatment, thionamide drugs are used in high doses. As thyroid hormone levels and the patient's symptoms normalize, the dose can be gradually reduced to the minimal effective one (so called titration regimen). Apart from the titration regimen, some clinicians employ the block-replace regimen which involves using a combination of high doses of a thionamide drug and levothyroxine. High doses of thionamides completely suppress endogenous production of thyroid hormones, whereas levothyroxine is administered to compensate the loss of endogenous thyroid hormone production. This regimen is rarely used, but can be helpful for patients who fluctuate between hyperthyroidism and hypothyroidism on thionamide monotherapy (3, 12-14).

3. *Apart from thionamides, what other drugs are used for the treatment of GD?*

Thionamide drugs inhibit the production of thyroid hormones by blocking the thyroperoxidase enzyme. For this reason, their therapeutic effects are delayed and several weeks of continuous use are usually necessary for existing thyroid hormone reserves to be depleted. To bridge this period, adjuvant drugs are commonly used in the treatment of GD, most importantly antagonists of  $\beta$ -adrenergic receptors ( $\beta$ -blockers).  $\beta$ -blockers lead to a rapid relief of hyperthyroid symptoms, such as palpitations and tremor. Propranolol is most commonly used for this purpose (its non-selective blockade of both  $\beta_1$  and  $\beta_2$ -receptors could be potentially advantageous). However, cardioselective  $\beta_1$ -blockers (atenolol, bisoprolol) can also be used. In addition, propranolol (at higher doses) inhibits peripheral conversion of T<sub>4</sub> to T<sub>3</sub>, which may potentially contribute to its beneficial effects in hyperthyroid patients. Apart from  $\beta$ -blockers, non-dihydropyridine calcium channel blockers (verapamil or diltiazem) can also be used to alleviate cardiovascular manifestations of GD (in cases of contraindications or intolerance to  $\beta$ -blockers), as well as benzodiazepines to relieve anxiety symptoms and difficulties with sleeping (3, 12-14).

4. *How is GD treatment with thionamide drugs monitored?*

When thionamide drugs are used for GD treatment, the efficacy is assessed by measuring FT<sub>4</sub> levels every 4-8 weeks until normalization is achieved (thereafter levels can be monitored less frequently, about every 8-12 weeks). TSH levels are also measured; however, TSH levels can remain suppressed for several months following the initiation of drug treatment, and low TSH levels in the starting phases of treatment are not necessarily a sign of inefficacy of thionamide drugs (13, 14).

5. *How long should GD patients use thionamide drugs and can these drugs lead to permanent recovery from GD?*

Adult patients with GD should receive thionamide drugs for at least 12-18 months (longer treatment duration is also possible). Thionamide drugs have immunomodulating properties (they reduce the level of anti-TSH receptor autoantibodies) and can induce complete remission of GD in about 50% of treated adult patients. Risk factors for relapse following treatment discontinuation are high serum levels of anti-TSH receptor antibodies, high thyroid volume and FT<sub>4</sub> levels at diagnosis, smoking, male sex and presence of orbitopathy. Before discontinuing thionamide drugs, levels of anti-TSH receptor antibodies should be measured in order to assess the risk of relapse. If levels of these antibodies are still high, there is a substantial risk of GD relapse and the patients should continue to use thionamide drugs or be subjected to definitive treatment options for GD (surgery or RAI) (3, 12-14).

In pediatric GD, thionamide drugs should be used for at least 36 months, seeing as shorter treatments are associated with a high risk of relapse. Even after this period, the rates of complete remission are lower than in adult patients (about 20-30% after two years of treatment); for this reason, longer treatment duration of 5 years is employed in patients with a high risk of relapse (15).

6. *What advice regarding the safety of thionamide drugs should be given to patients?*

The most common adverse effects associated with thionamide use are rash, urticaria and joint pain (fever and transient leukopenia are also possible). Rash and other minor cutaneous adverse effects can be managed effectively with antihistamines if needed. Substituting one thionamide drug with another is also an option if the cutaneous adverse effects do not resolve spontaneously.

The most serious and potentially life-threatening adverse effects of thionamide drugs are agranulocytosis and liver damage. Agranulocytosis (low neutrophil levels) can develop rapidly, and routine monitoring of complete blood counts is usually not useful in preventing this adverse effect (although complete blood counts should be performed before initiating thionamide therapy). For this reason, patients should be educated on how to recognize potential symptoms of agranulocytosis such as: fever, malaise, sore throat, bruising, mouth ulcers. Serious liver damage is more commonly associated with the use of propylthiouracil than with thiamazole. Children are more prone to this adverse effect and propylthiouracil is not used in pediatric GD patients. As in the case of

agranulocytosis, patients should be instructed to recognize symptoms associated with liver damage, such as nausea, vomiting, anorexia, pain in the upper abdomen, jaundice, general pruritus, dark urine (if these symptoms develop during the use of thionamide drugs, liver function tests should be performed). Patients who experience a serious adverse effect to a thionamide drug should not be switched to another thionamide, because of risk of cross-reactivity (3, 12-14).

More recently, the use of thiamazole/carbimazole has been associated with a small, but significant, risk of developing acute pancreatitis, a potentially life-threatening adverse effect. No such risk has been described for propylthiouracil (16).

*7. What are the contraindications for thionamide drugs?*

Thionamide drugs are contraindicated in patients with preexisting hematological conditions, as well as in patients with severe hepatic insufficiency. Additionally, thionamide drugs are contraindicated in patients who have previously experienced a severe adverse effect to thionamide drugs (9).

*8. Can thionamides be safely used during pregnancy and breastfeeding?*

GD should be treated during pregnancy if remission has not been achieved before conception. Uncontrolled thyrotoxicosis is associated with numerous adverse outcomes, such as miscarriage, gestational hypertension, premature birth, low birth weight, stillbirth and thyroid storm. Contemporary European and American guidelines recommend the use of propylthiouracil during the first trimester of pregnancy, because thiamazole can lead to serious birth defects. Propylthiouracil can also lead to birth defects; however, they are usually less severe than those associated with thiamazole. If the woman was using thiamazole before conception, she should be switched to propylthiouracil before becoming pregnant. During the second and third trimesters, as well as during breastfeeding, women can safely use thiamazole (6, 12-14).

*9. Can thionamide drugs be used for other forms of hyperthyroidism?*

Apart from GD, thionamide drugs can be used for the treatment of other forms of primary hyperthyroidism, such as toxic multinodular goiter and toxic adenoma. However, in these forms of hyperthyroidism thionamide drugs cannot lead to long-lasting remission and these forms of hyperthyroidism are usually treated surgically or with RAI (12, 13).

*10. How should Graves' orbitopathy be treated – non-pharmacological and pharmacological measures?*

Graves' orbitopathy is the main extrathyroidal complication of GD. Although relatively rare, this complication has significant effects on the quality of life of patients (even when mild) and is usually incompletely responsive to available treatment options. The usual signs/symptoms of this complication are retrobulbar pain, pain during eye movement, redness and swelling of the eyelids and conjunctiva, diplopia, retraction of the eyelids and exophthalmos (protrusion of the eyeball beyond the orbit). In severe cases,

Graves' orbitopathy may lead to eyesight loss due to corneal damage or optic nerve damage (12, 17).

Several non-pharmacological measures are useful in the treatment and prevention of progression of Graves' orbitopathy:

- Smoking cessation – Smoking increases the risk of orbitopathy development and progression, and smoking cessation should be encouraged in all patients with GD. Smoking also reduces the efficacy of immunosuppressive treatments used for orbitopathy, and increases the risk of orbitopathy progression following RAI treatment.
- Local treatments – Surface inflammation of the eye and dry eye are the most common GO symptoms. To alleviate these symptoms, patients may use artificial tears during the day and ophthalmic gels/ointments during the night while sleeping. Taping of the eyelids or using swimming goggles during sleep may also be helpful in patients with severe lid retraction to prevent ocular dryness.
- Selenium supplementation – In patient with mild forms of Graves' orbitopathy, 6-month selenium supplementation with sodium-selenite or seleniomethionine (with approximately 100 micrograms of selenium daily) can reduce the symptoms of orbitopathy and prevent the progression to more serious forms the disease (17).

More severe cases of Graves' orbitopathy require the use of immunosuppressive drugs (systemic or local glucocorticoids, mycophenolate, cyclosporine, azathioprine and others) or surgery/radiotherapy for treatment (17).

*11. When should hyperthyroid patients be referred to a doctor?*

Patients with GD who are treated with thionamide drugs should be instructed on how to recognize symptoms of agranulocytosis and liver damage (two serious adverse effects associated with thionamide drugs; see question 6). If these symptoms develop during treatment, the patients should discontinue the use of thionamide drugs and seek prompt medical attention from their doctor (9).

# F.A.Q. about Thionamide drugs



## What are the indications?

**Main: Graves` disease**

Additional: toxic multinodular goiter, toxic adenoma

## How to use?

**Oral use. Thiamazole is usually administered once daily (with food).**

**Propylthiouracil** is administered 2-4 times daily (depending on the dose)



## How long should thionamides be used?

**At least 12-18 months in adults**

Longer duration possible, if levels of anti-TSH receptor antibodies are still high after 12-18 months

## How to monitor efficacy?

**Measure hormone levels (FT4) every 4-8 weeks until euthyroid.** When euthyroidism is achieved, measure FT4 every 8-12 weeks

**Important:** TSH levels can remain suppressed for several months during treatment (low TSH is not necessarily a sign of inefficacy)



## Are thionamides safe?

Rash, urticaria and joint pain are most common adverse effects (usually mild)

**Agranulocytosis and liver damage (rare adverse effects) - educate patients how to recognize symptoms of agranulocytosis and hepatotoxicity**

## Should thionamides be used during pregnancy?

Hypothyroid women should use **propylthiouracil during the I trimester, and thiamazole during the II and III trimester** (thiamazole can cause serious birth defects if used during the I trimester). **Thiamazole is safe to use during breastfeeding**



Figure 2. Infographic with frequently asked questions (F.A.Q.) regarding thionamide drugs (13, 14)

Slika 2. Infografika sa najčešće postavljenim pitanjima u vezi primene tioamida (13, 14)

## Conclusion

Functional disorders of the thyroid gland are prevalent endocrine diseases and pharmacists in the community pharmacy are in an ideal position to help patients that are starting treatment for the first time. Key points to be covered with hypothyroid patients who are prescribed levothyroxine therapy are: when and how to use levothyroxine, how its effects are monitored and what drugs may affect its efficacy. Similarly, patients suffering from hyperthyroidism and who are prescribed thionamide drugs should receive information on: monitoring requirements, duration of thionamide therapy and how to recognize possible serious adverse effects associated with thionamide use. In addition, female patients with functional thyroid disorders who are planning to become pregnant should be informed on the importance of adequately treating both hypothyroidism and hyperthyroidism during pregnancy in order to reduce the risk of obstetric and neonatal complications.

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# **Funkcionalni poremećaji štitaste žlezde u farmaceutskoj praksi – kako možemo pomoći našim pacijentima?**

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## **Kratak sadržaj**

Funkcionalni poremećaji štitaste žlezde (hipotiroidizam i hipertiroidizam) spadaju u najčešće endokrine poremećaje sa kojima se farmaceuti svakodnevno susreću. Ovi poremećaji su veoma prevalentni u područjima sa adekvatnim unosom joda i pogađaju žene oko 10 puta češće nego muškarce. Hipotiroidizam (nedostatak tiroidnih hormona) je obično posledica Hašimotovog tiroiditisa, autoimunskog poremećaja koji dovodi do postepene destrukcije štitaste žlezde. Lek izbora za lečenje hipotiroidizma je levotiroksin, sintetski oblik hormona tiroksina. Ključne tačke o kojima treba razgovarati sa pacijentima kojima je prvi put propisan levotiroksin su kada/kako da se primeni ovaj lek, kako se prate njegovi efekti, koji lekovi mogu uticati na njegovu efikasnost i važnost pravilnog lečenja hipotiroidizma tokom trudnoće. Hipertiroidizam (povećana proizvodnja tiroidnih hormona) najčešće je uzrokovan Grejvsovom bolešću, još jednim autoimunskim poremećajem štitaste žlezde, u kojem stimulatorna autoantitela na TSH receptore dovode do povećane funkcije štitaste žlezde. Grejvsova bolest se najčešće leči tioamidima (tiamazol, karbimazol, propiltiouracil), a pacijenti koji koriste ove lekove treba da budu obavešteni o načinu praćenja efikasnosti, trajanju lečenja, kako da prepoznaju moguće ozbiljne neželjene efekte (agranulocitozu i hepatotoksičnost), kao i da se ovi lekovi moraju koristiti tokom trudnoće kako bi se smanjio rizik od štetnih ishoda za majku i bebu.

**Ključne reči:** hipotiroidizam, hipertiroidizam, levotiroksin, tioamidi

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