

Role of pharmacists in management of patients with thyroid disorders

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Abstract

Thyroid dysfunction is one of the most prevalent endocrine disorders, especially common in female patients. If patients are not diagnosed in time or adequately treated, the patients' quality of life can be significantly impaired and additional health problems may occur, considering the key roles of thyroid hormones in the body. Therefore, it is necessary to raise awareness about the importance of recognition of symptoms that may indicate a potential problem with the thyroid gland and help to identify possible causes. For patients who are already being treated with levothyroxine (hypothyroidism), or thiamazole, carbimazole or propylthiouracil (hyperthyroidism), it is necessary to point out the necessity of proper, regular use of the drugs and implementation of accompanying nonpharmacological measures, as well as the potential for the occurrence of adverse reactions and interactions with other drugs or food. A significant role in the mentioned activities should be played by the pharmacist, as the most accessible member of the health team, who can, if necessary, refer the patient to a doctor for diagnosis, monitor the effectiveness and safety of the therapy, and provide appropriate patient counseling.

Key words: hypothyroidism, hyperthyroidism, pharmaceutical care, patient counseling

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Introduction

Thyroid dysfunction is one of the most prevalent endocrine disorders, especially common in female patients (1). The primary function of the thyroid gland is the production and secretion of two major hormones into the bloodstream: triiodothyronine (T3) and thyroxine (T4). The secretion of T3 and T4 is regulated by thyroid-stimulating hormone (TSH) from the anterior pituitary, while TSH is regulated by thyrotropin-releasing hormone (TRH) (2-4). Any change in thyroid hormone levels that cannot be regulated properly will result in imbalanced hormone levels and some kind of disorder. Based on hormone levels, thyroid disorders can be classified into two large groups – hypothyroidism and hyperthyroidism. Both disorders can be caused by different factors, and problems can arise from: the thyroid gland itself, in which case it is classified as a primary disorder; the pituitary gland (secondary disorders); and the hypothalamus (tertiary disorders) (2, 3). The most common causes of hypothyroidism are inflammation and autoimmune disorders (e.g. Hashimoto thyroiditis), insufficient iodine intake, use of certain drugs, or lower sensitivity and response of peripheral tissues to the hormones (5, 6). On the other hand, the most common cause of hyperthyroidism is Graves-Basedow disease, but hyperfunctioning thyroid nodules are also a possible cause (2, 3, 7). If patients are not diagnosed in time or adequately treated, the quality of life can be significantly impaired and additional health problems may occur, considering the key roles that thyroid hormones play in the body, such as the regulation of metabolic processes, growth and development of the organism, influence on the cardiovascular system, maintenance of the normal function of the skeletal system and many others (2, 3, 8). While therapy of hypothyroidism is based on hormone substitution, in hyperthyroidism, in addition to drug therapy, radioactive iodine therapy and thyroidectomy are also available (2, 3). Pharmacists may play a significant role in managing thyroid conditions, especially when it comes to pharmacotherapy. Therefore, the aim of this article is to provide an overview of pharmacological therapy of thyroid disorders, as well as the role of pharmacists in managing these conditions.

Pharmaceutical care of patients with thyroid disorders

Pharmaceutical care is defined as the “responsible provision of drug therapy for the purpose of achieving definite outcomes that improve a patient’s quality of life” (9). Besides drug therapy provision, it includes a wide range of activities in which pharmacists can be included (10, 11). Due to ease of access, pharmacists practicing in community-based settings are often the first health care professional from which a patient seeks help. If a patient experiences symptoms that could be a sign of any kind of thyroid disorder, pharmacists should refer him or her to the doctor so that further diagnostic steps, such as laboratory testing or ultrasound examination, can be undertaken. Knowing what signs and symptoms to look for can be critical in identifying these patients. Patients with hypothyroidism show signs and symptoms such as: slower metabolism, weight gain, fatigue, constipation, dry skin, slowed heart rate, depression, inability to concentrate, edema of the skin and joints, puffy face, or poor mental development and growth in

children (2, 3, 6). On the other hand, signs and symptoms of hyperthyroidism include: warm and sweaty skin, weight loss, increased appetite, arrhythmia, tachycardia, palpitations, tremor, nervousness, anxiety and irritability, enlarged thyroid gland (goiter), protrusion of eyeballs (Graves' disease) (2, 3, 7).

If the patient already has a prescribed therapy, the pharmacist's role is even more important. In general, pharmaceutical care involves processes of designing, implementing, and maintaining a therapeutic plan, which includes the identification of actual or potential drug related problems, resolving identified and preventing new drug-related problems (11). Having in mind all the important characteristics of the patient, such as age, comorbidities, comedication and supplements that patient is taking regularly, the pharmacist can define a drug-related problem such as unnecessary drug treatment, inadequate drug treatment, inappropriate dosage, ineffective drug treatment, interaction, adverse drug event and poor adherence (4, 12, 13). Depending on its nature, a pharmacist can refer the patient back to the prescriber, or counsel the patient, providing education and useful advice about the therapy (14). Hence, pharmacological treatment of both disorders will be discussed in detail, with focus on the pharmaceutical care of patients treated with levothyroxine and antithyroid drugs, as well as the role of pharmacists in providing adequate information about nonpharmacological measures.

Levothyroxine

Therapy characteristics

Levothyroxine is identical to the natural thyroid hormone T4 and represents the standard replacement therapy when the body is deficient in the natural hormone (2). The goals of the therapy are resolution of symptoms and signs of hypothyroidism and normalization of TSH and thyroid hormone levels (15). It may also be used for euthyroid goiters or suppression therapy in thyroid carcinoma (16). Levothyroxine is converted to the more biologically active T3 in peripheral tissues, which is the main active form. Nevertheless, levothyroxine therapy is preferable to T3 replacement due to its slower onset of action, while T3 may be useful only when rapid effect is required (myxedema coma) (2, 3). In general, patients with overt hypothyroidism and subclinical form with TSH >10 mIU/L should be treated (6, 17).

Dose requirement of levothyroxine depends on age, characteristics of the disease, presence of cardiovascular disorder or other factors. The initial dose can vary from 25-50 µg in patients with mild or subclinical disease, to larger amounts in patients with negligible endogenous thyroid function. In general, full replacement dose of 1.6-1.7 µg/kg/day is usually required for an average adult with primary hypothyroidism and no history of cardiovascular disease (2, 6, 16, 18, 19). Regardless of initial symptomatic improvement, it may take several weeks before TSH levels recover fully. Therefore, TSH levels, and free T4 as needed, should be checked after 6-8 weeks of therapy initiation or dose alterations. If the desired TSH level is not reached, the dose should be adjusted

accordingly (3, 18, 19). After the achievement of desired values and resolution of symptoms, TSH should be checked once or twice per year (18, 19).

Precise dosing of levothyroxine is mandatory to prevent over- and under-treatment. Adverse effects of levothyroxine therapy are primarily those of hyperthyroidism due to excessive dosage, but under-treatment may also be common (19). Pharmacists should educate patients on how to recognize symptoms and notify the healthcare provider if they experience any of them (19). Although excessive levels of thyroid hormones may affect many organs and tissues, the main concern is related to the cardiovascular system and bones. There have been reports of increased risk of atrial fibrillation and reduced bone density (15). Hence, levothyroxine should be used with caution in elderly patients and patients with cardiovascular disorders. Finally, it is especially important to exclude glucocorticoid deficiency before initiating levothyroxine therapy in order to prevent acute adrenal insufficiency (2, 20).

Pharmacokinetic properties

After oral administration of a tablet, the bioavailability of levothyroxine is up to 80%. The drug is absorbed mostly in the small intestine (jejunum and upper ileum) and very little in the stomach (16, 19). However, low gastric pH appears to be a significant determinant of levothyroxine solubility and later absorption (16, 18). Peak serum concentration is reached 2 to 3 hours after administration (16). The bioavailability of levothyroxine is reduced in the presence of food and is increased by fasting (15, 19). Moreover, absorption may be decreased by ageing, drug-drug interactions, or in malabsorption conditions (19, 21, 22).

T4 is almost completely bound to plasma proteins, including thyroxine-binding globulin (TBG), thyroxine-binding prealbumin (TBPA), and thyroxine-binding albumin (TBA), with only 0.02-0.03% circulating freely (2, 16, 19). The bound hormone in plasma is in continuous and rapid exchange with the free fraction (19). The volume of distribution is 11.6 L in euthyroid subjects and 14.7 L in primary hypothyroid patients, which is similar to the volume of the extracellular fluid (16).

Levothyroxine is metabolized at the periphery by deiodination to equal amounts of T3 and inactive reverse T3 (rT3). The major site of degradation is the liver, but kidneys and other tissues are also involved, and both metabolites are further deiodinated (16). Conjugated metabolites with glucuronides and sulfates are eliminated by biliary secretion (2, 19). Levothyroxine is excreted in the urine as a free drug or deiodinated metabolites and conjugates, while a smaller portion of the dose is eliminated by feces (20). The half-life of levothyroxine is around 7 days, but may be shortened in hyperthyroidism or prolonged in hypothyroidism. The reported values of clearance were similar in hypothyroid and euthyroid subjects (16). Its relatively long half-life allows once-daily dosing, which is convenient for patients (15).

Levothyroxine formulation consistency

A particular challenge in long-term therapy is ensuring the consistency of levothyroxine formulation. Oral levothyroxine is usually administered in the form of tablets, which are available in multiple branded and generic preparations (15, 23). Although substitution between bioequivalent generic and branded products is often encouraged for many drugs, with certain medicines and in certain circumstances, it is better to avoid the risk. Drugs with narrow therapeutic range, such as levothyroxine, are particularly problematic (24). Even small variations in concentration may result in altered efficacy and adverse events. This may be a particular concern in vulnerable populations, such as elderly patients, pregnant women or children (24). In addition, baseline levels and feedback mechanism further complicate bioequivalence assessment of levothyroxine (15, 16, 23). Given the narrow therapeutic range and bioequivalence assessment issues, it is recommended, if possible, to keep patients on the same levothyroxine product. If the preparation is changed, TSH level monitoring in a few weeks and clinical evaluation of patient is required. The dose should be adjusted according to laboratory and clinical assessment (15, 23). Similarly, special concern is required when original products are reformulated, since different excipients can cause altered efficacy and adverse events (15, 23). Pharmacists should make sure that patients remain on the same levothyroxine preparation at every refill. If the patient needs to switch products due to supply problems or transition to a reformulated preparation, the pharmacist should advise him/her to measure their TSH levels after 4-6 weeks (15).

Influence of patient factors on pharmacokinetics and dosing

Physiological changes throughout life and acquired concomitant medical conditions may affect levothyroxine pharmacokinetics or require extra caution to avoid undesirable effects of therapy. Pharmacists should be aware of these factors, especially if they contribute to altered dose requirements, in order to monitor therapy in specific populations and identify patients who should be referred to a physician (18).

Physiologic changes during pregnancy require an increased availability of thyroid hormones to meet the needs of the mother and fetus. After conception, there is a rapid elevation in TBG concentrations, followed by a rise in total serum T4 level, while free T4 and TSH are decreased in the first trimester (16). In general, thyroid hormone requirements are increased by 20% to 40% during pregnancy (16, 25). In euthyroid women, the increased need is met by enhanced production of hormones. In hypothyroid women, requirements are similarly enhanced, often requiring an increase in levothyroxine dosage in order to maintain hormone levels within trimester-specific reference ranges (25, 26). The pharmacokinetics of levothyroxine is not only altered during pregnancy, but also more variable (16, 25). Interestingly, the median oral clearance was lower in pregnant than in nonpregnant women (25). Untreated or inadequately treated hypothyroidism presents a risk for both the mother and the fetus. Even subclinical hypothyroidism arising before conception or during pregnancy should be treated with levothyroxine (6, 26).

In general, infants and children may require higher doses per weight or per body surface area compared with adults. The dose for infants can be as high as 10-15 µg/kg daily for the first 3 months and it decreases towards adulthood (15, 16, 19, 20, 22). Some findings indicate a shorter half-life of T4 in euthyroid children compared to adults (27). On the other hand, in older patients, the elimination half-life is longer than in adults, metabolism of T4 to T3 is reduced, and absorption of T4 seems to be slightly reduced. Hence, elderly patients may require less levothyroxine than average adults (16). Moreover, they are more susceptible to the adverse effects of thyroid hormone excess, such as atrial fibrillation or osteoporotic fractures (15). To avoid precipitation of cardiac complications, in elderly and patients with cardiac disease therapy should be initiated in smaller doses, with gradual increases based on symptoms and serum TSH levels (3, 19, 20). It should be noted that normal serum TSH ranges are higher in older populations (15).

In obese patients, increased TSH levels do not necessarily indicate hypothyroidism, but may be related to leptin, a hormone produced by the adipose tissue. Previously, inconsistent findings about T4 and T3 values have been reported in obese patients (16). Santini et al. detected a significant positive correlation between the levothyroxine dose and total body weight. However, the association was much stronger when the levothyroxine dose was correlated with lean body mass than with fat mass (28). Hence, lean body mass might be a better predictor of levothyroxine dosage than actual body weight (16, 28).

Several gastrointestinal disorders, such as celiac disease, *Helicobacter pylori* gastritis, or atrophic gastritis, can compromise levothyroxine absorption. This is not surprising considering dominant absorption in the small intestine that is affected by gastric pH. Hence, an increased levothyroxine dose might be needed if these medical conditions are untreated (15, 16, 18, 22). On the other hand, no adjustment in levothyroxine dosing is required in cases of cirrhosis or renal failure (15). However, urinary losses of thyroid hormones in proteinuria associated with nephrotic syndrome may increase levothyroxine dose requirements (15, 16, 18).

Influence of drugs on thyroid function or levothyroxine pharmacokinetics

Many drugs may interfere with thyroid function or levothyroxine pharmacokinetics in various ways. Possible mechanisms include altered levothyroxine absorption, transport and metabolism, altered thyroid hormone synthesis or release, or changed TSH secretion (18). Table I presents common examples of interactions, while a more detailed discussion may be found elsewhere (2, 16, 21). Pharmacists should check for potential interactions with other drugs, suggest appropriate interventions, and refer the patient to a physician if necessary. Possible interventions may include avoiding concomitant use, levothyroxine dose modification, or careful monitoring of thyroid function (16).

Table I Drug effects on thyroid function and levothyroxine pharmacokinetics (2, 3, 16, 18)

Tabela I Uticaj lekova na funkciju tiroidne žlezde i farmakokinetiku levotiroksina (2, 3, 16, 18)

Effect	Drugs
Altered levothyroxine absorption	Calcium salts, aluminium hydroxide, ferrous sulphate, proton pump inhibitors, cholestyramine, sucralfate
Altered protein binding	Furosemide, salicylates, heparin, carbamazepine, phenytoin, androgens, glucocorticoids, estrogens
Altered metabolism	Amiodarone, glucocorticoids, propranolol, phenobarbital, carbamazepine, phenytoin, rifampin
Altered TSH secretion	Glucocorticoids, dopamine
Altered thyroid hormone synthesis or release	Iodide (amiodarone, contrast agent), lithium

Gastric acidity is important for levothyroxine solubility, which explains why some proton pump inhibitors may decrease its absorption (16, 19, 21, 22). Drugs containing aluminum, iron, calcium, cholestyramine or other ion exchange resins may also reduce levothyroxine absorption by creating insoluble complexes or interfering in a pH-related fashion (16, 19, 21). Hence, pharmacists should advise patients to separate their intake by 4 hours or more (16, 20).

Reduced protein binding was related to furosemide, salicylates, heparin, carbamazepine and phenytoin. Furthermore, androgens, anabolic steroids and glucocorticoids are associated with decreased serum TBG concentration and hormone binding. Conversely, estrogen increases TBG concentration and binding to this protein (2, 3, 16, 19, 20). Estrogen-containing products, such as hormone replacement therapy and oral contraceptives, may increase levothyroxine dosage requirements (16, 18, 20).

Medications that decrease TSH secretion may lead to lower thyroid hormone levels, which is rarely clinically important. On the other hand, hormone synthesis may be affected by lithium, iodine or amiodarone intake. Interestingly, iodide and amiodarone may induce both hypothyroidism and hyperthyroidism (2, 3, 16, 18). Amiodarone and glucocorticoids may also reduce the conversion of T4 to T3, as well as propranolol. Conversely, phenobarbital, phenytoin, carbamazepine and rifampicin increase hepatic

metabolism of thyroid hormones (2, 16, 19, 20, 22). These drugs may increase levothyroxine requirements in hypothyroidism (19, 20). Finally, tyrosine kinase inhibitors can have multiple effects, including an increased metabolism of levothyroxine, causing the need for dose elevation (18).

Although drug-drug interactions mostly include those affecting levothyroxine, pharmacists should bear in mind that this hormone may influence other drugs as well. For instance, levothyroxine may decrease the effect of antidiabetic drugs, but also increase the response to anticoagulants (warfarin) by displacing them from binding sites on proteins. If necessary, the dose of these drugs should be modified (19, 20).

Patient counseling

Pharmacists are in the position to monitor efficacy, safety and adherence of levothyroxine therapy and to provide appropriate patient counseling. Most patients require lifelong treatment with levothyroxine. In general, patients in long-term treatment are at a higher risk for low adherence (2). On the other hand, levothyroxine has some advantages. Due to its long half-life, it can be given once daily, and this simple regimen is convenient for patients. However, regular administration usually decreases over time, especially after the resolution of symptoms (2, 15). Hence, poor adherence remains a major challenge in the managing of long-term therapy. Pharmacists should educate patients about the disease and treatment, as well as about the consequences of irregular administration (2). If poor adherence is persistent regardless of counselling, a possible solution is supervised weekly dosing of oral levothyroxine (2, 15, 18). In addition, information about proper use of levothyroxine with regard to meals should be provided, considering the impact of food on drug bioavailability. Hence, pharmacists should advise patients to take levothyroxine firstly in the morning with water 30 to 60 minutes before breakfast, or at least 3 hours after the evening meal. Certain foods, such as soybeans and dietary fibers, should be especially avoided (15, 19). Moreover, pharmacists should advise patients about the importance of consistency of levothyroxine formulation, which has previously been explained in detail (23). Finally, monitoring safety and drug-drug interactions, as well as appropriate counseling about them, is also an important element of pharmaceutical care (2, 10).

Antithyroid drugs

Indication and dosage

Antithyroid drugs, which operate by inhibiting thyroid hormone synthesis, are intended for the treatment of hyperthyroidism (2, 29). Thioamides, which are represented by methimazole (MMI), carbimazole and propylthiouracil (PTU), act by inhibiting thyroid peroxidase, which is responsible for iodine organification and synthesis of thyroid hormones (29, 30). These drugs cannot, however, affect the liberation of already synthesized hormones or interact with exogenously administered levothyroxine (31, 32). MMI and PTU are the most commonly available, whereas carbimazole (methimazole prodrug) is available only in some countries (33). Both MMI and PTU are equally

effective; however, MMI is more commonly used due to a better safety profile and favorable pharmacokinetics (2, 29).

These drugs are used for the management of hyperthyroidism, including the treatment of Graves' disease and thyrotoxicosis (only PTU in cases of excessive hormones release, since it inhibits the peripheral conversion of T4 to T3); amelioration of hyperthyroidism in preparation for surgical treatment; an adjunct to radioactive iodine therapy; in juvenile hyperthyroidism, to delay ablative therapy and to manage thyrotoxic crisis (only PTU) (31, 32, 34). The dosing regimens for hyperthyroidism for each drug are presented in Table II. The initial dose should be gradually reduced as the condition improves (35). Since carbimazole is less commonly prescribed and is a prodrug which, during absorption, completely converts to MMI (36), it will not be discussed further in the article. It is generally recommended to limit treatment duration to 12-24 months continuously. However, some studies suggest that long term use could be justified (37).

Table II Dosing regimens of thioamides (31, 32, 34)

Tabela II Režimi doziranja tionamida (31, 32, 34)

Drug	Initial dose	Maintenance dose	Children*	Renal impairment	Liver impairment	Pregnant and breastfeeding women
Methimazole	10-40 mg/day	2.5-10 mg/day (5-20 with levothyroxine)	0.5 mg/kg/day divided into 2/3 doses (max 40 mg/day)	Monitoring	Lowest dose possible (lower clearance)	Lowest dose possible (2.5-10 mg/day)
Carbimazole	20-60 mg divided into 2/3 doses	5-15 mg/day (20-60 with levothyroxine)	15 mg/day	/	/	The lowest effective dose
Propylthiouracil	300-450 mg divided into 3 doses (max 600-900)	50-150 mg divided into 3 doses	5-7 mg/kg every 6-8 h	GFR 10-50 ml/min: 75% dose GFR <10 ml/min: 50% dose	Caution: lower dose might be recommended	The lowest effective dose

*for methimazole and carbimazole children over 3 years old, for propylthiouracil over 6 years old

Pharmacokinetic properties

PTU and MMI both follow linear pharmacokinetics. The absorption of both drugs is rapid and complete; however, MMI exhibits considerable interindividual variability

(38). Unlike MMI, PTU is highly bound to plasma proteins (>75%) (35). Both drugs accumulate in the thyroid gland, which is important since inhibition of iodide organification depends on intrathyroidal rather than plasma concentration. Concentrations in breast milk are very low, but both drugs cross the placenta (38).

Data on peripheral metabolism are limited, but prolonged elimination of MMI in liver failure is expected (Table II) (35). Metabolism in the thyroid gland involves binding to thyroglobulin and subsequent oxidation. Both drugs undergo enterohepatic circulation, since fecal excretion is very low. The main metabolite of PTU is an inorganic sulfate, but it is also rapidly glucuronidated and excreted by bile back into the intestine, where it is available for reabsorption (39). In urine, small amounts of unchanged drugs are excreted together with mainly glucuronides and other metabolites. The longer half-life of MMI (6-8 hours) than PTU (1.5 hours) enables a favorable dosing regimen of MMI (35). In pregnancy, the half-life of MMI is expected to be shortened (38).

Special populations and interactions

In pregnant patients, the distribution of antithyroid drugs didn't change significantly (comparable values for total volume of distribution), but based on the significantly reduced value of MMI half-life (2 hours), this drug has a higher clearance due to overall increased metabolism rate in pregnancy (40). Nevertheless, both drugs should be administered in the lowest effective dose (Table II) to ensure safety of the fetus. However, PTU is preferred during the first trimester of pregnancy (35). Even though both drugs are excreted in breastmilk, women should breastfeed while on antithyroid treatment, since both drugs are classified as very low risk for the infant (41).

Children should receive both suggested drugs in doses weight-related to the adult dose (Table II), since no significant differences in drug pharmacokinetic or pharmacodynamic behavior are expected (36). However, PTU should be avoided in children and adolescents due to hepatotoxicity (35). PTU was studied in the elderly population and no significant changes were observed for the distribution or elimination of the drug. However, the absorption rate was three times slower (42). Accumulation of the drug is, therefore, not expected, so the dosing regimen doesn't differ from the adult one. Nevertheless, the manufacturer recommends that these patients should be monitored more closely, and individualized dosing is advised (31, 32).

In liver failure, higher circulation levels of MMI are expected in accordance with extensive hepatic metabolism, so a lower dose is suggested (Table II) (31). As for PTU, only monitoring is advised, since metabolism in the liver isn't as extensive (32). In patients with renal failure, insufficient data regarding MMI pharmacokinetics have led to a recommendation for closer monitoring of these patients and individualized dosing, while patients on PTU should be given the appropriate dose based on estimated glomerular filtration rate - eGFR (Table II) (31, 32).

There aren't many clinically significant interactions with antithyroid drugs. Most significant interactions are linked to the disease status and thyroid hormone levels. Beta blockers, which are used as additional treatment for tachycardic patients, and theophylline

may have altered clearance in patients with hyperthyroidism. Therefore, should the patient become euthyroid, it might be necessary to adjust the dose (32). Moreover, hypothyroid patients are more sensitive to digoxin, whereas the hyperthyroid ones are resistant to its effect, so monitoring is advised (32). Since overall metabolism is increased in patients with hyperthyroidism, coagulation factors metabolism might be increased, so during concomitant treatment patients should be advised to increase the dose of oral anticoagulants or monitor blood clotting parameters more frequently (32).

Adverse events and contraindications

Should adverse reactions to antithyroid drugs occur, they most usually manifest in the beginning of the treatment (first 4 months). The most common side effects are maculopapular rashes and urticaria (10% of patients), arthralgia and gastrointestinal disturbances (1-5% of patients), fever and joint swelling; less common ones include taste perversion, hepatic impairment, lymphadenopathy, vasculitis and loss of scalp hair (reversible after discontinuation) (36, 43). Minor cutaneous reactions may resolve spontaneously, but in some patient antihistamine therapy or substitution with another antithyroid drug may be needed. However, substitution is not recommended in the case of a serious allergic reaction (35). The most serious but luckily less common adverse event is suppression of the bone marrow, in the form of reversible leucopenia or agranulocytosis (1% of patients), sometimes aplastic anaemia and thrombocytopenia (36, 43). Agranulocytosis is probably autoimmune-mediated and accompanied by fever and sore throat, so all patients should be advised to pay more attention and inform their physician immediately if the symptoms arise. Since this side effect develops rapidly (within 2-3 days) blood cell count should be performed before treatment initiation and if symptoms occur (35). Since cross reactivity of these drugs has been confirmed, in the event of discontinuation of one antithyroid drug due to agranulocytosis, the use of the other one instead is contraindicated (43). Among serious side effects, liver impairment and vasculitis are of note. PTU has a slightly higher probability to cause liver damage by inflicting hepatocellular injury, whereas MMI usually causes cholestatic jaundice or toxic hepatitis (43, 44). Liver function tests should be performed, especially in patients receiving PTU. Nevertheless, elevated enzymes can be expected during treatment, so discontinuation is advised only if they are accompanied by symptoms or if enzyme elevation is higher than 5 times (30). Vasculitis is also more common in patients on PTU treatment, and should be treated with high doses of corticosteroid or cyclophosphamide in severe cases (43). As a result of inadequate dosing or overtreatment, goiter and hypothyroidism are an excessive therapeutic effect of both drugs (36), but the risk was found to be higher for patients on MMI (44).

Both drugs are contraindicated in the case of previous severe hypersensitivity reaction (e.g. agranulocytosis, hepatitis, vasculitis, nephritis) or severe adverse reactions during previous treatment with either drug (31, 32). Additionally, for MMI severe hepatic insufficiency, existing cholestasis or acute pancreatitis in anamnesis are remarked (31).

During pregnancy, combined administration of thyroid hormones and antithyroid drugs is not recommended (35).

Patient counseling

Although only endocrinologists may alter dosing regimens and change the course of treatment, pharmacists have a crucial role in monitoring and advising patients receiving antithyroid treatment. In the primary health care setting, the pharmacist should check dosing regimens, perform medication reconciliation, verify medication compliance and communicate any treatment concerns to the healthcare team (45). When a patient comes to claim either PTU or MMI, the pharmacist should assess if the treatment was effective during the previous period by asking about hormone levels or disease symptoms. Thyroid function tests should be performed 3-4 weeks after treatment initiation (since most patients become euthyroid within that period), then monthly, and when TSH levels increase to a reference range – every 3-6 months (35). Patients should have reminders set if multiple daily doses are administered. However, MMI is usually prescribed once daily to improve adherence, and should be administered in the morning after breakfast with a full glass of water (31).

Every patient should be informed about the most common and serious side effects of these drugs and report them immediately. Agranulocytosis and liver failure should be singled out and explained in detail. If the patient notices a fever, sore throat, weakness, or a headache, total and differential cell counts should be obtained to rule out agranulocytosis (45). Liver function tests should be advised if the patient experiences jaundice, light-colored stools, or dark urine (35). If the patient is or plans to get pregnant, the pharmacist should refer them to their doctor for a change of therapy (45).

Nonpharmacological measures

When advising a patient regarding nonpharmacological measures, pharmacists should mainly focus on the proposed diet, dietary supplements and lifestyle changes that the patient should implement in their everyday life to ensure better treatment outcomes. Thyroid disorders cannot be treated without pharmacological therapy; however, patients should nevertheless be advised to lead a healthy lifestyle and have a balanced diet (46). Meals should be diverse, taken in correct portions, rich in soluble fiber (plant-based foods, whole-grain cereal), with limited amounts of unsaturated oils and enough ω -3 fatty acids. Five portions of fruit or vegetables should be consumed every day, as well as dairy or dairy alternatives and plenty of fluids (minimum 6-8 glasses) (46). An anti-inflammatory diet can also be advised, since some nutrients (magnesium, dietary fiber, fatty acids, resveratrol, gingerol, shogol, paradols, ω -9 monounsaturated fatty acid, ω -3, flavonoids and modified citrus pectin) reduce inflammation and re-establish hormonal balance (47, 48). If a deficiency of a nutrient, vitamin or mineral is present, supplementation can be suggested. Vitamin D deficiency is common among these patients, so 10 μ g per day can be prescribed (46).

Iodine supplementation should be avoided for patients in treatment. Since in most countries iodination of salt is mandatory, there is no need for additional consumption, which could even become harmful for the thyroid (49). Since zinc is necessary for the synthesis of thyroid hormones, while selenium potentially has immunomodulatory effects, these micronutrients are often used as supplements (48, 50). However, according to the American Thyroid Association, the usage of dietary supplements, nutraceuticals, or other over-the-counter products either in euthyroid individuals or for treating hypothyroidism is not recommended (15).

Conclusion

Thyroid disorders are common in clinical practice and the number of patients is constantly increasing, especially in the female population. While therapy of hypothyroidism is based on substitution with levothyroxine, three different approaches are available in hyperthyroidism, including antithyroid drug therapy, radioactive iodine therapy and thyroidectomy. Pharmacists have a significant role in managing thyroid conditions, especially when it comes to pharmacotherapy. They are well-positioned to provide education and counseling of patients about the disease, correct use of therapy and importance of adherence. In addition, pharmacists may have an important role in identifying patients that should be referred to a physician. Finally, monitoring the efficacy and safety of therapy, as well as management of drug interactions, is a fundamental part of the pharmaceutical care concept.

Conflicts of interest

The authors declare that they have no conflict of interest.

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Uloga farmaceuta u zbrinjavanju pacijenta sa poremećajem rada tiroidne žlezde

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Kratak sadržaj:

Poremećaj funkcije tiroidne žlezde spada u najčešće endokrine poremećaje, posebno u ženskoj populaciji. Ukoliko se poremećaj ne ustanovi na vreme i ne leči adekvatno, kvalitet života pacijenta može biti narušen i može doći do dodatnih zdravstvenih problema, s obzirom na ključne uloge koje tireoidni hormoni imaju u organizmu. Stoga je neophodno podići svest o važnosti prepoznavanja simptoma koji ukazuju na potencijalni problem sa štitnom žlezdom, kao i moguće uzroke. Kod pacijenata koji su na terapiji levotiroksinom (hipotireoidizam) ili tiamazolom, karbimazolom ili propiltiouracilom (hipertireoidizam), potrebno je ukazati na značaj pravilne i redovne upotrebe lekova, uz sprovođenje pratećih nefarmakoloških mera, i ukazati na potencijal za pojavu neželjenih reakcija i interakcija sa drugim lekovima/hranom. Značajnu ulogu u navedenim aktivnostima bi trebalo da ima farmaceut, kao najdostupniji član zdravstvenog tima, koji može uputiti pacijenta lekaru radi postavljanje dijagnoze, pratiti efikasnost i bezbednost terapije, i pružiti pacijentu adekvatno savetovanje.

Ključne reči: hipotireoidizam, hipertireoidizam, farmaceutska zdravstvena zaštita, savetovanje pacijenata
