International Journal of Research in Pharmacy and Pharmaceutical Sciences
www.pharmacyjournal.in
ISSN: 2455-698X
Received: 25-11-2024, Accepted: 26-12-2024, Published: 10-01-2025
Volume 10, Issue 1, 2025, Page No. 17-22

Recent overview: Medication use for hyperthyroidism

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Abstract
Excessive thyroid hormone production is the hallmark of hyperthyroidism, a disorder that seriously compromises systemic and metabolic health. Pharmacological treatments that restore hormonal balance are the mainstay of effective management. New insights into hyperthyroidism have improved treatment strategies, increasing patient safety and effectiveness. First-line treatments include antithyroid medications like Propylthiouracil (PTU) and Methimazole, which efficiently lower hormone synthesis. Although PTU is only used in certain circumstances, such as the first trimester of pregnancy, Methimazole is typically used because of its better safety profile and ease of dosage. Beta-blockers, such as Propranolol, are commonly used as adjunctive therapy to provide quick symptom alleviation for conditions like tachycardia and tremors.
The new developments in the treatment of hyperthyroidism center on individualized therapy, taking into account variables including age, comorbidities, and the severity of the condition. Furthermore, pharmacogenomics developments are starting to affect medication choice and dosage, lowering side effects and enhancing therapeutic results. Notwithstanding these developments, difficulties still exist, especially when it comes to treating refractory patients and preventing long-term issues. In order to provide more efficient and patient-centered care, research is still being done to refine current therapy paradigms and investigate new therapeutic targets. This summary emphasizes the value of treating hyperthyroidism using a multidisciplinary approach that incorporates both comprehensive patient management techniques and pharmaceutical breakthroughs.

Keywords: Hyperthyroidism, thyroid gland, grave's disease, endocrine disorder, metabolism, thioamides

Introduction

The anterior neck contains the thyroid gland, a midline tissue. As an endocrine gland, the thyroid produces calcitonin and thyroid hormone, which help control growth, metabolism, and serum levels of electrolytes like calcium. The thyroid gland can be affected by a variety of disease processes, and changes in hormone production can lead to either hyperthyroidism or hypothyroidism. Inflammatory conditions like thyroiditis, autoimmune diseases like Grave's disease, and tumors like papillary thyroid carcinoma, medullary thyroid carcinoma, and follicular carcinoma are all related to the thyroid gland [1].

According to pathology, hyperthyroidism refers to the thyroid gland's overproduction and secretion of thyroid hormone. Excess thyroid hormone circulation, regardless of the cause, is known as thyrotoxicosis. The extrathyroidal supply of thyroid hormone or the release of performed hormone into the bloodstream with poor thyroid radioactive iodine uptake are the two main causes of thyrotoxicosis without hyperthyroidism. Hyperthyroidism brought on by elevated serum levels of thyroid hormones, such as thyroxine (T4), triiodothyronine (T3), or both, and decreased serum levels of thyroid stimulating hormone (TSH). Other causes include excessive synthetic thyroid hormone, toxic adenoma, multinodular goiter, thyroid inflammation, and excessive iodine consumption [2]. There are two types of hyperthyroidism: overt and subclinical. Low levels of thyroid-stimulating hormone (TSH) and elevated levels of thyroid hormones, such as thyroxine (T4), triiodothyronine (T3), or both, are hallmarks of overt hyperthyroidism. Serum TSH levels are low in subclinical hyperthyroidism, while T4 and T3 levels are normal [3].

The origins and severity of hyperthyroidism determine how it should be treated. Treatment options for hyperthyroidism include radioiodine therapy, thyroid surgery, and antithyroid medications. Hyperthyroidism can also be treated with antithyroid medications like methimazole. β-blockers are another option for symptom management. Surgery to remove the thyroid is mostly used for cancerous diseases. Women are typically affected more frequently than men, especially those between the ages of 20 and 40. While autoimmune thyroid disorders, such as Hashimoto's thyroiditis and Graves' disease, occur most frequently in iodine-replete populations, nodular thyroid disorders are more common in iodine shortage [4].

Grave's disease: In regions with adequate iodine, Grave's disease is the most frequent cause of hyperthyroidism. Autoantibodies that bind and activate the thyrotropin receptor (TSHR) are the primary mechanism of responsibility. Despite the relative prevalence of Graves hyperthyroidism, there are currently no effective treatments for the condition. Radioactive iodine, surgery, and antithyroid medications, which lower thyroid hormone synthesis, are established therapy techniques. However, recent clinical studies have explored new medications that inhibit the immunological mechanism or target the primary autoantigen (peptides, small compounds, or monoclonal antibodies). [5]

Toxic multinodular goiter: The antecedent of hyperthyroidism is toxic multinodular goiter. It is brought on by the thyroid gland's numerous independently functioning nodules releasing thyroid hormones without cause. It is also common in geriatrics (poor diet) and in areas with dietary iodine deficit (third-world countries). Among the elderly, TMNG is more prevalent than Graves' illness [6].

Toxic nodular goiter (toxic adenoma): The most common precursor of thyrotoxicosis in the elderly, particularly in iodine-deficient regions, is toxic nodular goiter. According to certain research, solitary poisonous nodules are more common in women than in males, with a 1:5 M: F ratio. A distinct thyroid mass that functions independently of pituitary regulation is known as an autonomous thyroid nodule (toxic adenoma) [4, 7].

Subacute thyroiditis: A viral infection, particularly (though not solely) of the upper respiratory tract, or post-viral inflammation are the causes of subacute thyroiditis (SAT), sometimes referred to as De Quervain or granulomatous thyroiditis. There is a 5/1 female to male ratio and an annual incidence of 12.1/100,000 individuals [8].

Suppurative thyroiditis: Compared to the clinical forms of subacute thyroiditis and Hashimoto's thyroiditis, acute suppurative thyroiditis (ST) is far less common, especially in youngsters. Many noninfectious inflammatory disorders might have symptoms that are similar to those of infectious thyroiditis. For these infections to be treated quickly, it is crucial to recognize their bacteriological and clinical characteristics [9].

Drug induced hyperthyroidism:

Amiodarone induced hyperthyroidism (AIH): A strong class III anti-arrhythmic medication with beta-blocking capabilities is amiodarone. A 100-mg tablet contains 250 times the daily recommended iodine need, demonstrating its high iodine content. In euthyroid patients, amiodarone causes distinctive changes in thyroid function testing. It is essential to comprehend these changes in order to prevent needless tests and treatments. Both the compound's direct toxic effects on thyroid parenchyma and its iodine content contribute to amiodarone-induced thyroid dysfunction. Amiodarone-induced thyrotoxicosis is more challenging to diagnose and treat than amiodarone-induced hypothyroidism [10].

Iodine induced hyperthyroidism: The Jod-Basedow phenomenon, or iodine-induced hyperthyroidism, is prevalent in older adults with chronic nodular goiter and in areas experiencing chronic iodine deficiency that are receiving iodine supplements. The elderly who may have concomitant heart disease and those with little access to healthcare are the main targets of iodization initiatives, which may raise the risk of iodine-induced hyperthyroidism. [4, 11]. Patients with iodine-deficiency goiter, euthyroid subjects who have previously experienced instantaneous and iatrogenic episodes of thyroid malfunction, patients with multinodular goiters who live in areas of iodine replacement or inadequacy, and people without a confirmed underlying thyroid condition may all experience iodide-induced hyperthyroidism [12].

Postpartum thyroiditis: The first year following delivery or an abortion is when postpartum thyroiditis (PPT), a syndrome of temporary or permanent thyroid dysfunction, occurs. With a prevalence ranging from 5 to 9%, it is the most prevalent thyroid condition during the postpartum phase. Essentially, it is an autoimmune thyroid inflammation brought on by modifications to the humoral and cell-mediated immune responses. Its typical biphasic course consists of a brief bout of thyrotoxicosis followed by either temporary or permanent hypothyroidism [13].

Pathophysiology: The hypothalamus, pituitary gland, and thyroid gland are all part of a delicate negative feedback loop that controls the secretion and release of thyroid hormones. TRH is released by the hypothalamus, which stimulates the pituitary to release TSH, which in turn causes the thyroid gland to release T4 and T3, two thyroid hormones. The hypothalamus and pituitary glands often suppress the release of TRH and TSH, respectively, when thyroid hormone production is elevated. When this sensitive system is upset, more thyroid hormone is secreted and released, which results in hyperthyroidism. Pituitary tumors that secrete TSH produce a hormone that is biologically active and resistant to normal feedback control. Iodine is necessary for the thyroid gland to secrete thyroid hormones [6, 14].

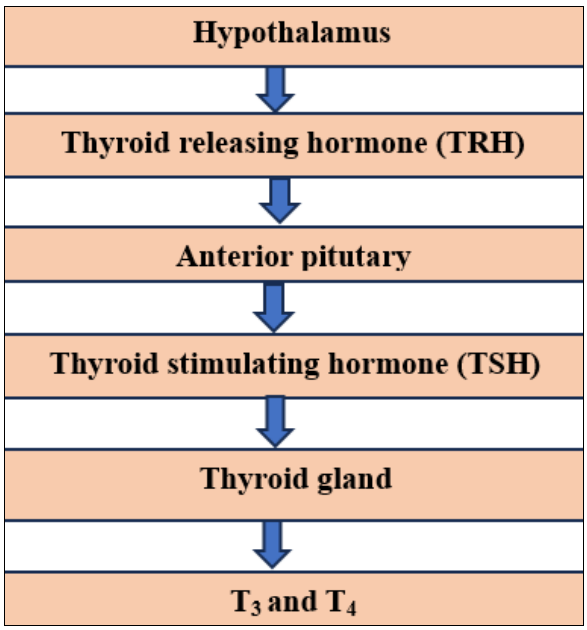

Fig 1: Pathophysiology of Hyperthyroidism

Symptoms of hyperthyroidism:

Frequent bowel motions, weight loss (or gain, in certain situations), difficulty sleeping, difficulty tolerating heat, weakening in the muscles, difficulty swallowing, or neck fullness are all signs of hyperthyroidism. Physical symptoms include redness on the palms of your hands, loosening of your nails, hives, patchy hair loss, twitching in your face and limbs, and a noticeable enlargement of the thyroid gland (goiter).

Diagnosis:

Blood tests: Thyroid hormone levels, T4 and T3, are measured by blood tests; these levels must be elevated in order to diagnose hyperthyroidism. Thyroid stimulating hormone (TSH) levels are also assessed. TSH is low while T4 and T3 levels are high in hyperthyroidism.

Iodine uptake scan: By measuring the amount of iodine that the thyroid gland absorbs, this test assesses thyroid function. On an empty stomach, patients get a little amount of radioactive iodine. Over the following few hours, the iodine is either eliminated in the urine or concentrated in the

thyroid gland. Next, the quantity of iodine that enters the thyroid gland is measured.

Thyroid scan: Because it also needs the patient to absorb radioactive iodine, which then accumulates in the thyroid gland, this test is usually conducted concurrently with the iodine uptake test. Gamma rays released by radioactive iodine are used in thyroid scans to provide an image of the thyroid.

Treatment

Monitoring the state of hyperthyroidism with medication, radioiodine, or surgery is the aim of management. Normalizing thyroid hormone production, reducing symptoms and long-term effects, and offering tailored treatment based on the patient's age, gender, non-thyroidal conditions, and response to prior treatment are the goals of treatment for hyperthyroidism. Thyroid surgery, radioactive iodine, antithyroid medicines, and symptom-controlling pharmaceuticals are some of the treatment options [15].

Non-Pharmacologic Therapy: Thyroid gland removal surgery is recommended for patients who have a big gland (>80 g), severe ophthalmopathy, and no remission. Although thyroid surgery is quick and efficient, it is also costly and intrusive. Prior to surgery, the patient must be euthyroid. It may result in temporary hypocalcemia that necessitates calcium supplements as well as lifelong hypothyroidism. The effectiveness of radioactive iodine therapy and antithyroid medications has reduced the need for surgery. In the past, the most common cause of thyroid storm, which had a 50% fatality rate, was stress during surgery in the operating room. With preoperative treatments like propranolol, antithyroid drugs, and iodine, thyroid storm during surgery is now extremely uncommon. Propylthiouracil or methimazole is typically administered until the patient is biochemically euthyroid (generally six to eight weeks) if a thyroidectomy is planned. Iodides (500 mg/day) are then added 10 to 14 days before to surgery in order to de-escalate the gland's vascularity. While the thioamides are being used, levothyroxine may be given to maintain the euthyroid condition [15].

Antithyroid pharmacotherapy

Using thioamides to decrease thyroid hormone synthesis is the cornerstone of medication therapy. Antithyroid drugs are thought to last between twelve and eighteen months [15]. Hyperthyroidism and Graves' disease are treated with thioamide antithyroid medications such as methimazole and carbimazole. By preventing thyroid peroxidase from doing its job, they lower the production of thyroid hormones.

Thioamides: The thioamides, PTU, and MMI are the most widely used antithyroid medications. PTU and MMI prevent the production of thyroid hormones by inhibiting the thyroid gland's peroxidase enzyme system, which stops trapped iodide from being oxidized and then incorporated into iodotyrosines and eventually iodothyronine (a process known as "organification"); they also prevent the coupling of MIT and DIT to form T4 and T3, and PTU (but not MMI) prevents the peripheral transformation of T4 to T3. The thyroid aggressively concentrates MMI and PTU in opposition to a concentration gradient. Their main function is to prevent the production of hormones both inside and outside the thyroid [16-17]. Antithyroid drugs can be used to treat hyperthyroidism initially (long-term therapy: one to two years) or as a prelude to surgery or radiometabolic treatment (short-term therapy: weeks or months). Mild to moderate hyperthyroidisms, a modest increase in gland volume, children or adolescents, pregnancy or lactation, and ophthalmopathy that could be exacerbated by radiometabolic treatment are among the elective indications for pharmaceutical treatment [16].

Table 1: Dosage Strength brand name of Thioamides

Drug Name	Dosage Form	Dose	Brand Name
Methimazole	Tablet	Mild: 15 mg/day PO divided q8hr initially Moderate: 30-40 mg/day PO divided q8hr initially Severe: 60 mg/day PO divided q8hr initially Maintenance: 5-30 mg/day PO divided q8hr	Tapazole Tapdin Northyx Methimez ®10 Methimercazole® 10
Carbimazole	Tablet	Starting dose for adults is between 20mg and 60mg a day, split into 2 or 3 smaller doses. Children usually start on 15mg a day, split into 2 or 3 smaller doses.	Neo-Mercazole® 5 Neo-Mercazole ®10 Neo- Mercazole® 20 Thyracab MT-Carbimazole
Propylthiouracil	Tablet	300-450 mg/day PO divided q8hr initially Maintenance: 100-150 mg/day divided q8hr	Procarbizole Propycil® 50

Table 2: Difference between Methimazole and Propylthiouracil

Methimazole	Propylthiouracil
inhibits the conversion of T4 to T3.	No restriction on the conversion of T4 to T3
Has inhibition of thyroid peroxidase	Has inhibition of thyroid peroxidase
Half-life (6-8 hours)	Half-life (1-2 hours)
Increased patient compliance	Patient compliance is worse.
Possesses significant intrathyroidal storage	Possesses minimal intrathyroidal storage

Radioactive Iodine Therapy: For the past 80 years, RAI-131 therapy has been the most popular and well acknowledged treatment for hyperthyroidism. RAI-131 therapy has changed how patients and doctors view available treatments, from the benign nature of hyperthyroidism to malignant neoplasms and their

metastases. It was initially used as a treatment for benign thyroid illness in 1941. The FDA approved it in 1971 for the treatment of well-differentiated thyroid carcinoma, toxic diffuse and nodular goiter, and non-toxic nodular goiter [20]. Oral sodium iodide 131 accumulates in the thyroid and mainly inhibits hormone secretion by combining with thyroglobulin and thyroid hormones. RAI is the preferred treatment for toxic multinodular goiters, toxic autonomous nodules, and Graves' disease [6, 18].

Antithyroid drugs of second choice

Potassium perchlorate

Ionic inhibitors called perchlorates prevent iodine from entering thyrocytes, which prevents the production of thyroid hormones. However, in contrast to other pharmacological and non-pharmacological treatments, perchlorates are not regarded as the first-line treatment for hyperthyroidism and thyrotoxicosis [21]. Since the 1950s, it has been widely recognized how perchlorates impact thyroid function and their potential as a treatment for thyroid dysfunction [22].

When used orally, it is quickly absorbed from the gastrointestinal tract. Particularly in type 1 amiodarone-induced thyrotoxicosis, perchlorate can be used to treat thyrotoxicosis caused by an excess of exogenous iodine. By competitively associating with NIS, the medication competitively reduces iodide uptake in the thyroid gland. It can also discharge iodine from the thyroid gland, lowering intrathyroidal iodine and accelerating the release of thyroid hormones. Oral administration of 250 mg every 6 hours is the initial dosage [16, 18, 23].

Beta blockers

Increased sympathetic activity precedes several hyperthyroidism symptoms, including sweating, anxiety, tremor, and palpitations, which can be quickly managed with beta blockers. When taken in relatively high quantities (more than 160 mg daily), propranolol can slightly inhibit the conversion of T4 to T3. To improve medication compliance, beta blockers such atenolol 50–100 mg or nadolol 40–80 mg can be administered once day. While waiting for the results of antithyroid medications, beta blockers are used in the first few weeks of controlling hyperthyroidism, provided there are no contraindications, such as asthma [18]. When treating Graves' disease or toxic nodules, preparing for surgery, or treating thyroid storm, β-Blockers are typically used as an adjuvant therapy in conjunction with antithyroid drugs, RAI, or iodides. It is only used as a first line of treatment for thyroiditis and hyperthyroidism brought on by iodine [16].

Lithium carbonate

Lithium carbonate comes in two forms: immediate-release and sustained-release. After delivery, the plasma concentrations of the immediate-release and sustained-release formulations peak approximately 1-2 and 4-5 hours, respectively. Lithium is completely eliminated by the kidneys and has a half-life of 18 to 36 hours. With aging and renal failure, lithium clearance is considered to de-escalate. The thyroid gland, most likely by active transport, concentrates lithium three to four times as much as the plasma does. Lithium works by preventing TSH from acting on cAMP, which suppresses the release of thyroid hormones. It's possible that lithium inhibits the production of thyroid hormones. Lithium carbonate side effects include mild, moderate, and severe toxicity, which are signs of persistent intoxication. Myoclonic twitches, nystagmus, dysarthria, ataxia, and disorientation are signs of moderate toxicity (level 2–2.5 mEq/L), whereas nausea, vomiting, diarrhea, hand tremor, and drowsiness are signs of mild toxicity (lithium level 1.5–2 mEq/L). Seizures, coma, death, impaired consciousness, and renal failure are examples of severe toxic symptoms (level > 2.5 mEq/L) [18, 23].

Glucocorticoids

The primary way that glucocorticoids regulate thyrotoxicosis is by inhibiting the peripheral conversion of T4 to T3. When iodine causes a destructive effect on thyroid tissue, as occurs in the early stages of subacute thyroiditis or in type-2 amiodarone-induced thyrotoxicosis, glucocorticoids are utilized. Oral glucocorticoids are used to treat Type 2 AIT, whereas thioamides are used to treat Type 1 AIT. Glucocorticoids have two effects: they reduce peripheral T4 to T3 conversion and have an anti-inflammatory effect [16, 18].

Cholestyramine

T4 is sequestered in the colon and its excretion in the feces is increased by the ionic exchange resin cholestyramine. The liver contains the majority of T3 and T4, which are also secreted in the bile in conjugated form and in trace amounts in unconjugated form. In the large intestine, bacterial enzyme deconjugation releases free hormones, which are then reabsorbed into the bloodstream to complete the enterohepatic circulation of thyroid hormone. It has been demonstrated experimentally that 50 mg of cholestyramine can bind roughly 3000 lg of T4, which in turn can speed up the thyroid hormones' clearance. There have been attempts to use ionic exchange resins to sequester thyroid hormones in the colon due to the increased enterohepatic circulation of these hormones during hyperthyroidism [23, 24].

Iodine-containing compounds

In the 19th century, burnt sponge extract was supplanted as a treatment for endemic goiter by iodine solutions, such as potassium iodide solution (SSKI) or potassium iodide-iodine solution (Lugol's solution). They were also occasionally used to treat Graves' illness, but by the end of the century, they were viewed as a risky treatment. Before the thionamides were developed, they were the only treatment for moderate hyperthyroidism in the 1930s. They gained popularity again in the 1920s as a preoperative treatment for hyperthyroidism. Iodine still plays a little part in the management of hyperthyroidism nowadays. To make SSKI, KI crystals are added to water until the KI saturation point is reached. Iodide's predominant effects on the thyroid include a temporary decrease in thyroid hormone secretion (the acute WolffChaikoff effect) and inhibition of thyroid hormone release from the thyroid gland. Iodide prevents thyroglobulin proteolysis and the release of T4 and T3, and it also temporarily lowers the amount of thyroid hormone produced. Iodide is used to treat thyroid storms and get ready for emergency procedures before surgery [18, 23].

Novel Approaches of Drug Delivery for the Hyperthyroidism:

1. Transdermal drug delivery system

Using Franz cells cultured *in vitro*, methimazole gels and organogels demonstrated excellent drug penetration through the skin [25]. When compared to the parent drug, the methimazole prodrug showed increased skin permeability [26].

2. Oral and buccal drug delivery systems

The clearest example of this is propylthiouracil, which needs several dosages per day and has a hepatotoxic reputation due to its fast release and absorption. As a result, patients may benefit greatly from the creation of propylthiouracil formulations with prolonged release [27]. Another option to oral medicine administration is buccal drug delivery. By eliminating drug instability in the GI tract and related first-pass metabolism, this method can be utilized for systemic drug administration [28]. The controlled release profile of coated buccal tablets for systemic methimazole administration was demonstrated [29].

3. Nanotechnology

Drugs for various routes of administration and the treatment of numerous acute and chronic illnesses have been developed using the nano method. Nanotechnology contains a variety of platforms, including as liposomes, dendrimers, micelles, nanoconjugates, polymeric nanoparticles (nanocapsules and nanospheres), nanosponges, and nanoparticles. A prodrug of methimazole, carbimazole is used to treat Grave's disease and hyperthyroidism. The polymeric nanospheres of Carbimazole provide the sustained release effect and lowering the dose frequency [30].

4. Sustained release drug delivery:

The majority of medications are made using traditional techniques for efficient drug delivery; nevertheless, some therapeutic agents need to be modified because they are unstable or have limited therapeutic ranges. These by creating continuous release drug delivery, issues were resolved. A potential strategy for sustained release medicine delivery reduces the frequency of doses while also delaying drug release. Because sustained release medication administration lengthens the drug's residence period, it efficiently increases absorption [31].

Future perspective

1. Artificial intelligence (AI)

The intricacy of diagnosing certain thyroid disorders has prompted the creation of artificial intelligence (AI) tools to help doctors. In addition to providing new tools for clinical research, customized treatment, and medical diagnostics, artificial intelligence (AI) is revolutionizing healthcare. When diagnosing and tracking diseases, thyroid function tests are a valuable tool for doctors. It is obvious that artificial intelligence systems can help doctors and laboratory medicine specialists with assay design, process optimization, decision-making, test prescription, and interpretation [32].

Abbreviations

TSH: Thyroid stimulating hormone	**TRH:** Thyroid releasing hormone
T_4: Thyroxine	**MIT:** Monoiodotyrosine
T_3: Triiodothyronine	**DIT:** Diiodotyrosine
TSHR: Thyrotropin receptor	**PTU:** Propylthiouracil
TMNG: Toxic multinodular goiter	**MMI:** Methimazole
SAT: Subacute thyroiditis	**CBZ:** Carbimazole
ST: Suppurative thyroiditis	**RAI:** Radioactive iodine therapy

Acknowledgement

I want to express my sincere gratitude to the management and principal of SVPM College of Pharmacy in Malegaon (Bk II), Baramati, Pune, for giving all the resources needed to finish this review work.

Conclusion

In conclusion, this article provide a comprehensive overview of Hyperthyroidism disease, encompassing its pathology, pathophysiology, causes, medication. It also give insight into medicines and treatment used for treatment of Hyperthyroidism, exploring classes of drugs which are used to treat the hyperthyroidism, their targets, agents, mechanisms of action, and notable side effects. Additionally, it focuses on the current therapies and treatment options, including drug & its dosage forms along with its route of administration. Furthermore, it explores the innovative realm of drug delivery methods. incorporating novel drug delivery systems for enhanced medical intervention.

Conflict of Interest

All Authors declared that there is no conflict of interest.

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