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LEVOTHYROXINE IN FOCUS: DRUG INTERACTION RISKS AND ADVERSE EVENTS – A COMPREHENSIVE REVIEW

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ABSTRACT

Levothyroxine (LT4) is a cornerstone therapy for hypothyroidism and related thyroid disorders. Despite its efficacy, levothyroxine is highly susceptible to drug interactions and dosing errors, which can lead to suboptimal treatment outcomes or serious adverse effects. This review highlights the common drug interactions that impair LT4 absorption, including proton pump inhibitors, calcium and iron supplements, antacids, and various systemic medications. These interactions may cause elevated TSH levels and persistent hypothyroidism. Conversely, excessive LT4 dosing can result in hyperthyroid-like symptoms, thyrotoxicosis, cardiovascular complications, osteoporosis, and neuropsychiatric disturbances. Particular attention is given to mechanisms of interaction, clinical evidence, and strategies to mitigate adverse outcomes. The review emphasizes the importance of individualized dosing, patient education, and regular monitoring of thyroid function to optimize LT4 therapy and reduce the risk of adverse drug reactions.

KEYWORDS: Levothyroxine, Hypothyroidism, Drug interactions, Proton pump inhibitors, Calcium supplements, Iron supplements, Adverse drug reactions.

INTRODUCTION

Levothyroxine (LT4), a synthetic form of the thyroid hormone thyroxine (T4), is the cornerstone therapy for the management of hypothyroidism, goiter, and differentiated thyroid cancers. With a long-standing record of clinical efficacy, affordability, and once-daily dosing convenience, LT4 has become one of the most frequently prescribed medications worldwide. Administered orally in doses typically ranging from 1.6 to 1.8 µg/kg/day, LT4 is effective in

restoring euthyroid states and improving quality of life in affected individuals. Despite these advantages, levothyroxine therapy is far from straightforward and presents several clinical challenges that require careful consideration.[1]

One of the most important concerns in levothyroxine therapy is its narrow therapeutic index. Small deviations in dosing or absorption can result in under- or overtreatment, both of which carry clinical consequences. A growing body of evidence has highlighted the high prevalence of drug-drug and drug-food interactions that interfere with LT4 absorption and bioavailability. These interactions often go unnoticed, resulting in fluctuating thyroid hormone levels and suboptimal disease control.[2] Several commonly used agents including proton pump inhibitors (PPIs), calcium and iron supplements, antacids, antiepileptic drugs, and antidepressants have been shown to significantly impair LT4 absorption in the gastrointestinal tract or alter its metabolism, leading to elevated TSH levels and persistent hypothyroid symptoms.

Large scale observational studies support the clinical relevance of these interactions. A UK based retrospective analysis found that nearly 59% of patients on LT4 were taking at least one concomitant medication, with statins (17.6%), PPIs (13.6%), and calcium supplements (6.8%) being the most common. Similarly, a Colombian database study reported that 68.5% of LT4 users were also on other medications, most frequently antiulcer agents (44%), hypoglycemics (17.4%), and iron supplements (16.1%). These findings underscore the widespread risk of interaction-related treatment inefficacy. If even one in five patients is affected by such interactions, a significant proportion up to 12–15% may have inadequately controlled thyroid function despite adherence to prescribed LT4 doses.[3]

Beyond drug interactions, dietary and gastrointestinal factors can further influence LT4 pharmacokinetics. Certain foods and beverages, as well as underlying conditions such as gastritis, celiac disease, and lactose intolerance, may alter gastric pH or bind directly to the drug, reducing its solubility and absorption. This is why LT4 is typically advised to be taken on an empty stomach, at least 30–60 minutes before meals or other medications. The development of liquid and soft gel LT4 formulations has helped overcome some of these bioavailability barriers by bypassing the need for gastric dissolution. While under-treatment due to impaired absorption is common, the opposite scenario excessive LT4 dosing can be equally harmful. Supratherapeutic doses can mimic hyperthyroidism, leading to symptoms such as palpitations, nervousness, weight loss, insomnia, and heat intolerance. More seriously, prolonged overexposure may cause atrial fibrillation, hypertension, reduced bone mineral density, and even thyrotoxicosis a potentially life-threatening condition characterized by severe metabolic and cardiovascular derangements.[4]

The clinical complexity of levothyroxine therapy necessitates a comprehensive understanding of its pharmacological profile, potential drug and food interactions, and risk of adverse drug reactions (ADRs). Diagnosis of LT4-related interactions typically involves detailed patient history, medication review, and sometimes specific testing such as the LT4 absorption test or drug withdrawal trials.

DRUG –DRUG INTERACTIONS

The gastric pH can be changed by medications.

Tablet dissolution, which increases solubility by removing sodium ions, requires a physiological gastric pH. Absorption is improved when the pH is elevated, as happens in cases of autoimmune gastritis and H. pylori infection.[5,6]

The ionization status at various environmental pH levels explains the phenomenon. Duodenal and gastric ulcer treatment involves the use of proton pump inhibitors (PPIs) and hydroxide antagonists (H+ secretion reducers).[7]

The solubility of LT4 tablets may be affected by these medications.

Inhibitors of the Proton Pump

Patients taking LT4 and proton pump inhibitors are treated together in 13.6% of cases.[8] The initial report of PPI-induced LT4 absorption impairment was made in 2006 by Centanni et al. This retrospective study used data from a single institution to examine the effects of concurrent administration of omeprazole and LT4 on ten patients diagnosed with nontoxic multinodular goiters. During routine follow-ups, patients taking omeprazole had significantly higher TSH levels (1.7 vs. 0.1 mU/L, p=0.002). Another team of researchers that same year also used a 4-week washout period and randomized, open-labeled crossover design to study 20 volunteers.[9] The subjects were given 4 µg/kg of LT4 mixed with 40 mg of pantoprazole, or without it. For the first three hours, samples were taken every fifteen minutes. For the following seven hours, samples were taken every sixty minutes. The levels of serum free T4, total T4, and TSH were not significantly different in the 10-hour LT4 absorption test. Additionally, the drug's interaction was not supported by a 2008 prospective self-control study.[10] PPIs had contradictory effects on LT4. Potentially different medications with different long- or short-term effects might account for the difference. Furthermore, the healthy volunteers' thyroid functions are within the normal range, which allows them to make up for the reduced LT4 absorption. More information is provided by recent studies are a related randomized, open-labeled, crossover, two-arm study with 24-hour LT4 absorption tests was carried out by Yue et al. in 2015 with 16 healthy individuals. In either Period One or Period Two, these individuals were administered intravenous injections of esomeprazole. The AUC0-12h dropped to 83.22% ($p<0.1$), and the maximum concentration (Cmax) dropped to 87.32% of what it was with LT4 alone.[11]

In addition, the drug interaction between proton pump inhibitors and LT4 was supported by multiple retrospective studies with large samples. Nevertheless, conflicting findings were found in an additional prospective study with 21 hypothyroid patients. There was no statistically significant difference in the slightly elevated TSH levels observed in patients treated with 20 mg or 40 mg of omeprazole.[12] Finally, the drug's interaction was supported by six out of the nine clinical studies mentioned earlier. Only one of the three papers dealing with omeprazole's long-term effects found a statistically significant increase in TSH. There is no statistically significant difference in the other two investigations that used LT4 absorption tests. The drug interactions were further supported by another systematic review.[13] In addition to their alkalizing effects, proton pump inhibitors (PPIs) boost biliary clearance of LT4 by inducing UDP-glucuronosyltransferase, which in turn reduces absorption.[14] Because of Hashimoto's thyroiditis, the female patients were given LT4 doses. Once she started taking 40 mg of omeprazole daily, her TSH level jumped over the normal range. Without adjusting the dosage, she switched from LT4 tablets to soft-gel capsules, and the hypothyroid symptoms went away and the TSH went down.[15]

Antagonists for Histamine H2-Receptors

H2 antagonists have the same indications as proton pump inhibitors. Twenty people were randomly assigned to either cimetidine/ranitidine or a placebo in a 1992 study by Jonderko et al. that tested 4-hour LT4 absorption. It was found that cimetidine significantly reduced AUC (371±72 vs. 467±82, $p<0.01$), but ranitidine had no effect (477±132 vs. 459±109, $p>0.05$).[16] The interaction between famotidine and LT4 was examined sixteen years later in a clinical trial

that used comparable designs and settings. In terms of pharmacokinetic characteristics, no discernible difference was found. Additionally, the interaction was not supported by a retrospective database study using a large database [17] Therefore, how the two medications interact with one another is a mystery. Changing to a different H2-antagonist may help a patient whose LT4 malabsorption is thought to be caused by cimetidine.

C-Reactive Vitamin

An over-the-counter drug that is commonly used is vitamin C, which can increase the production of gastric acid. We hypothesize that it improves LT4's efficacy by increasing gastric dissolution. A prospective pre-post study involving 28 hypothyroid patients was carried out by Antúnez et al. for a duration of 6 weeks. The TSH levels were markedly decreased following the consumption of 1 g/day of vitamin C (9.01±5.51 vs. 2.27±1.61 mU/L, p<0.0001). People with gastritis or proton pump inhibitors (PPIs) who have an elevated gastric pH may be able to eliminate their malabsorption problems by taking vitamin C. In 2014, Jubiz et al. found evidence that backed up the theory. For two months, they had 31 individuals with hypothyroidism and gastritis take 500 milligrams of vitamin C daily. After taking vitamin C with it, the median TSH level dropped from 11.1 to 4.2 mU/L (p=0.0001). Vitamin C has shown promise as a treatment for LT4 malabsorption caused by an elevated stomach pH.[18]

Calcium Supplements

A UK population study found that calcium supplements are the third most prescribed concomitant medication for LT4 patients. Some 6.8% of patients took calcium supplements for osteoporosis. Schneyer reported the first LT4-calcium drug interaction in 1998. [19] The three patients in this report eliminated malabsorption by stopping calcium salts or adding dosing intervals. Singh and colleagues recruited 20 hypothyroid patients in 2000. Patients with stable LT4 doses and normal thyroid hormone levels received 1200 mg of calcium with levothyroxine in the morning on an empty stomach. The calcium dose was followed by thyroid tests two and three months later. Calcium was stopped, and thyroid functions were monitored for two months. Calcium intake resulted in lower Free T4 and total T4 levels (1.22±0.05 vs 1.41±0.06 ng/dL, p<0.001, 8.55±0.41 vs 9.31±0.39 µg/dL, p=0.03) and higher TSH levels (2.71±0.43 vs 1.44±0.21 mU/L, p=0.008) Radioisotope-labeled LT4 was diluted in calcium carbonate buffer. After 2 hours incubation and 10 minutes centrifugation, they took supernatant samples. At pH 2.0, the supernatant had less than 60% LT4.[20] Unexpectedly, pH 7.4 LT4 molecules were unbound. In vitro experiments confirmed LT4-calcium complexing. A randomized crossover study by the same researchers confirmed the interaction a year later. Singh et al. recruited seven healthy individuals to receive 1000 µg oral LT4 with or without 2.0 g of calcium carbonate. Two LT4 absorption tests (dosing on an empty stomach and testing thyroid functions for 6 hours) were done with a 1-month washout. Dosing calcium supplements simultaneously reduced LT4 absorption by 31.0% (579 vs. 837 µg). A study using the same methods found that calcium carbonate and other supplements (e.g., calcium citrate and calcium acetate) interact.[21]

According to Zamfirescu et al, calcium acetate did not affect TSH levels in a retrospective long-term study.[22] According to Diskin CJ et al, the discrepancy may be due to study design and duration. Several observational studies and case reports support the oral LT4-calcium supplement interaction. Several methods can eliminate calcium supplement malabsorption. We could assume that most calcium-treated hypothyroid patients remain euthyroid without medical intervention since few have reported clinically significant TSH elevation. Sometimes a dose increase is enough to induce euthyroidism. In cases of severe TSH elevation or malabsorption, we recommend dosing separation or

discontinuing interfering medications. Diskin et al. suggest switching calcium supplements to similar products. Since disintegration was not required, novel LT4 formulations (liquid solution and soft-gel capsule) have been shown to avoid calcium-induced malabsorption. Compared to the tablet group, the solution group had significantly lower TSH levels (8.74±7.2 vs. 2.15±1.4 mU/L, p<0.001). New formulations were promising in these studies. Concomitant gastrointestinal diseases can worsen malabsorption, so eradicating them should also be considered.

Iron Supplement

Another common LT4 inhibitor is ferrous sulfate. An analysis of ~30,000 hypothyroid patients in Colombia found that 16.1% also took iron salts. Citation 4 The iron-LT4 interaction was discovered earlier. Campbell et al. gave 14 hypothyroid patients ferrous sulfate with LT4 for 12 weeks in 1992. After the observation, the serum TSH increased from 1.6±0.4 to 5.4±2.8 mU/L. An iron-thyroxine experiment outside a living organism showed a purple complex that didn't dissolve, suggesting iron bound to LT4. TSH levels were elevated in two pregnant women receiving ferrous sulfate for anemia.[23] Like calcium supplements, iron-induced malabsorption is treated. Separating dosing and stopping iron supplements usually cures malabsorption. You can also avoid the issue orally. According to Benvenga et al., the solution group had lower TSH levels than the tablet group when ingesting simultaneously (8.74±7.2 vs. 1.68±0.9 mU/L, p<0.001). Citation 17 Thyroid hormones must be monitored until they reach target levels.[24,25]

Drugs that affect systemic LT4 transport

Serum carriers such as TBG, albumin, and transthyretin bind approximately 99.8% of T4 and T3. bind over 80% of thyroid hormones. Hypothyroxinemia results from elevated TBG, which lowers free T3 and T4. Reducing TBG works oppositely. Pregnant women and those with cirrhosis require more LT4. [26,27] Elevated serum TBG from estrogen may be the cause. The 2001 Arafah study included 25 hypothyroid postmenopausal patients with estrogen indications.Citation 6666 Thyroid hormone levels were measured before and 12 weeks after estrogen treatment. The TBG increased from 20.8±3.1 to 30.8±4.0 mg/L after 12 weeks (p<0.001). As a result, free T4 decreased from 1.7±0.4 to 1.4±0.3 ndL, dL, and TSH increased from 0.9±1.1 to 3.2±3.1 mU/L (p<0.001). In 483 estrogen-dosing LT4 patients, TSH was elevate Citation 3on 3 If combined, estrogen supplements can raise serum TBG, lower free T4 and T3, and cause hypothyroxinemia. Drug discontinuation and LT4 dose adjustment are needed to improve bioavailability. Carbamazepine, rifampin, and raloxifene may also raise TSH. After separate raloxifene and LT4 dosing, the elevated TSH levels returned to reference ranges. Drugs like carbamazepine treat seizures. Deluca et al. examined oral LT4's efficacy in five epileptic children in 1986. After two months of carbamazepine use, T4 levels dropped from 12.7±1.1 to 7.5±2.3 µg/dL. The T3:T4 ratio increased significantly (p<0.05), but T3 did not change. The accelerated turnover of T4 to T3 caused by carbamazepine likely caused persistent hypothyroidism. Sertraline and fluoxetine treat depression with selective serotonin reuptake inhibitors. A prospective study by de Carvalho et al. found that fluoxetine reduced T4 over 90 days and T3 transiently for 30 days in healthy voCitation 81Citation 81 Despite no significant difference in hypothyroid patients, fluoxetine was thought to activate deiodinase.[28]

ADVERSE DRUG REACTIONS

Patients who are diagnosed with hypothyroidism, goiter, or thyroid cancer are typically prescribed levothyroxine sodium, which is also referred to as Thyronorm. In spite of the fact that it is effective, taking the incorrect dosage can result in symptoms that are comparable to those of hyperthyroidism, in addition to having systemic effects. patients diagnosed with hypothyroidism, goiter, or thyroid cancer revealed that they are commonly prescribed levothyroxine

sodium, a synthetic form of the thyroid hormone T4. Commercially known as Thyronorm, this medication is the standard treatment for managing thyroid hormone deficiency and suppressing thyroid-stimulating hormone (TSH) in cases such as goiter and differentiated thyroid cancer. Levothyroxine works by restoring normal levels of T4, thereby helping to regulate metabolism, energy levels, and overall endocrine function.[29] While levothyroxine is generally effective when administered at the correct dose, improper dosing—either too low or too high—can lead to significant complications. In particular, excessive doses can mimic the symptoms of hyperthyroidism, including palpitations, weight loss, anxiety, insomnia, and heat intolerance. Moreover, prolonged overtreatment may contribute to systemic effects such as decreased bone mineral density, particularly in postmenopausal women, and increased cardiovascular risks, including arrhythmias and hypertension. Therefore, careful monitoring of thyroid function tests, including TSH and free T4 levels, is crucial to ensure optimal therapeutic outcomes and avoid adverse effects. A number of symptoms are associated with hyperthyroidism, which is a condition that affects both the endocrine and metabolic systems.

When levothyroxine is taken in excessive amounts, it can cause symptoms that are comparable to those of hyperthyroidism. This is because it causes the thyroid hormone receptors to be over stimulated. A decrease in body weight, an intolerance to heat, and increased sweating are some of the symptoms and the mechanism. Thyrotoxicosis is characterized by a severe overdose, which can lead to symptoms such as fever, delirium, and coma. Thyrotoxicosis is a condition that can be fatal. When the thyroid hormone receptors (TRα/TRβ) are overactivated, it results in the activation of several metabolic enzymes, such as the Na+/K+ ATPase and the cytochrome oxidases.[30]

Hyperthyroidism is a clinical condition characterized by excessive thyroid hormone activity, which affects both the endocrine and metabolic systems. It manifests through a wide range of symptoms due to the overstimulation of cellular metabolism. One potential cause of hyperthyroid-like symptoms is the excessive intake of levothyroxine, a synthetic thyroid hormone commonly used to treat hypothyroidism and related conditions. When taken in supratherapeutic doses, levothyroxine can overstimulate thyroid hormone receptors (TRα and TRβ), mimicking the physiological effects of endogenous hormone overproduction.

This overstimulation leads to increased expression and activation of several metabolic enzymes and pathways. For instance, enzymes such as Na^+/K^+-ATPase and mitochondrial cytochrome oxidases are upregulated, significantly enhancing cellular metabolic activity. As a result, patients may experience hallmark symptoms of hyperthyroidism, including unexplained weight loss, heat intolerance, excessive sweating, nervousness, tachycardia, and restlessness. In more severe cases, especially with prolonged or extreme overdose, a condition known as thyrotoxicosis can develop. Thyrotoxicosis represents an acute and potentially life-threatening state of excessive thyroid hormone action. Clinical manifestations can escalate to include high fever, profound agitation or delirium, cardiovascular instability, and in extreme scenarios, coma. If not promptly recognized and managed, thyrotoxicosis may be fatal, underscoring the importance of precise dosing and regular monitoring of thyroid function in patients on levothyroxine therapy.[31]

Considerations Regarding the Cardiovascular System

Thyroid hormones have significant effects on the cardiovascular system, primarily by increasing both the heart rate (a chronotropic effect) and the force of cardiac contractions (an inotropic effect). These actions are largely mediated through enhanced sensitivity to catecholamines, particularly by upregulating β-adrenergic receptors in the heart and vascular system. As a result, even normal levels of circulating catecholamines can produce exaggerated cardiovascular responses in hyperthyroid states or in patients receiving excessive doses of levothyroxine.

One of the most commonly observed clinical manifestations of this enhanced β-adrenergic activity is the occurrence of palpitations and tachycardia, which may be distressing to patients. In more severe or prolonged cases, the overstimulation of the cardiac conduction system can lead to arrhythmias, including atrial fibrillation (AF). Atrial fibrillation is particularly concerning in elderly individuals, where it significantly increases the risk of stroke and other thromboembolic events.[32] At the cellular level, thyroid hormones influence the expression and function of ion channels in cardiac myocytes, particularly those regulating potassium (K^+) and calcium (Ca^{2+}) flux. Changes in these ion currents can alter the duration of the cardiac action potential and the refractory period, creating a substrate for the development of arrhythmias. Elevated thyroid hormone levels promote increased Ca^{2+} influx and altered K^+ channel activity, which can lead to early or delayed afterdepolarizations, setting the stage for ectopic activity and reentrant arrhythmias.

Therefore, it is critical to monitor cardiac function in patients receiving thyroid hormone therapy, especially in older adults and those with pre-existing cardiovascular disease. Careful titration of levothyroxine dosage and periodic ECG monitoring can help minimize the risk of adverse cardiac events associated with thyroid hormone excess.[33]

Considerations Regarding the Gastrointestinal (GI) System

Thyroid hormones play a crucial role in regulating gastrointestinal (GI) function, and disturbances in thyroid hormone levels particularly excess levels seen in hyperthyroidism or thyrotoxicosis can significantly affect GI motility. One of the hallmark symptoms associated with this effect is diarrhea, which results from increased intestinal motility driven by the stimulatory action of thyroid hormones on smooth muscle tissue within the GI tract. Mechanistically, both triiodothyronine (T3) and thyroxine (T4) enhance the responsiveness of smooth muscle cells to neural and hormonal signals. They exert their effects, in part, by upregulating serotonin (5-HT) receptors, particularly the 5-HT3 and 5-HT4 subtypes, which are heavily involved in the regulation of intestinal peristalsis. Serotonin acts as a key neurotransmitter in the enteric nervous system, and its receptors play a critical role in modulating gut motility, secretion, and sensation.[34] By increasing the expression and sensitivity of these receptors, thyroid hormones accelerate peristalsis, leading to reduced intestinal transit time—the time it takes for food to pass through the digestive system. This rapid transit can impair water reabsorption in the colon, resulting in frequent, loose stools, a common complaint in patients with hyperthyroidism or those taking excessive doses of levothyroxine. Clinically, this symptom can contribute to dehydration, electrolyte imbalances (such as hypokalemia), and malabsorption if not appropriately managed. Therefore, awareness of GI symptoms like diarrhea is important when assessing thyroid function and adjusting thyroid hormone therapy, particularly in patients presenting with unexplained gastrointestinal disturbances.[35]

Effects on the Nervous and Psychiatric Systems

Thyroid hormones play a critical role in maintaining normal neurological function and mental health. In states of excess—such as hyperthyroidism or excessive levothyroxine dosing—patients often exhibit neuropsychiatric symptoms including anxiety, tremors, irritability, restlessness, and insomnia. These symptoms are linked to alterations in central nervous system (CNS) neurotransmitter dynamics, particularly involving noradrenaline (norepinephrine) and serotonin, both of which are essential for mood regulation, sleep, and motor control.

Thyroid hormones, especially T3 (triiodothyronine), can cross the blood-brain barrier and directly affect neuronal activity. Within the brain, T3 influences gene expression related to neurotransmitter synthesis, receptor sensitivity, and synaptic transmission. Elevated thyroid hormone levels enhance adrenergic tone, which can amplify the effects of

noradrenaline, resulting in heightened arousal and anxiety. Simultaneously, thyroid hormones may impact serotonin pathways, potentially contributing to mood disturbances, sleep dysregulation, and decreased emotional resilience. These neurochemical changes explain the frequent psychiatric manifestations observed in patients with thyrotoxicosis or poorly managed thyroid hormone therapy.

Effects on the Musculoskeletal System

The musculoskeletal system is also affected by prolonged thyroid hormone excess. One of the most clinically significant consequences is the development of osteoporosis, a condition marked by decreased bone mineral density and increased fracture risk. Chronic exposure to high levels of T3 stimulates bone resorption by promoting osteoclast activity, the cells responsible for breaking down bone tissue.

This process is mediated primarily through the upregulation of RANKL (Receptor Activator of Nuclear Factor Kappa-B Ligand), a key signaling molecule that binds to its receptor RANK on osteoclast precursors, stimulating their differentiation and activation. Over time, the enhanced resorption outpaces bone formation, leading to net bone loss. This mechanism explains why patients on long-term supraphysiologic doses of levothyroxine—especially postmenopausal women—are at an elevated risk of developing osteoporosis and related complications. Therefore, careful dosing and routine monitoring of bone health, including bone mineral density (BMD) testing, should be considered in patients receiving long-term thyroid hormone therapy, particularly those with additional risk factors for bone loss.

Managing Adverse Reactions to Levothyroxine Therapy

Levothyroxine, while highly effective in treating hypothyroidism and related thyroid disorders, can lead to adverse drug reactions if not properly dosed. These reactions can range from mild to severe, depending on the degree of thyroid hormone excess. Management strategies should be tailored to the severity of symptoms and biochemical markers, especially thyroid-stimulating hormone (TSH) levels.

1. Moderate Adverse Drug Reactions (Due to Overdose)

In cases of mild to moderate adverse effects such as palpitations, nervousness, or mild insomnia associated with suppressed TSH levels, the most appropriate course of action is to adjust the levothyroxine dosage downward. Clinical guidelines recommend a reduction of 12.5 to 25 micrograms per day, depending on the degree of TSH suppression and patient symptoms. This approach helps restore a euthyroid state while minimizing the risk of overtreatment. Continued monitoring is essential to ensure TSH levels return to the target range.

2. Severe Adverse Drug Reactions (Thyrotoxicosis)

In more serious cases, such as overt thyrotoxicosis, patients may experience severe symptoms like tachycardia, tremors, significant weight loss, or agitation. In these instances, immediate intervention is necessary. A beta-blocker, most commonly propranolol, is the first-line treatment to manage cardiovascular symptoms, particularly tachycardia and hypertension.

Simultaneously, it is recommended to discontinue levothyroxine temporarily to allow thyroid hormone levels to normalize. Therapy can be reinitiated at a lower dose once TSH levels and clinical symptoms stabilize. According to Ross DS et al. (2016), this approach is effective in preventing complications and reestablishing hormonal balance.

3. Monitoring and Preventive Measures

To prevent adverse effects and ensure optimal therapy, regular monitoring of thyroid function is essential. TSH levels should be evaluated every 6 to 8 weeks following initiation or adjustment of therapy until a stable maintenance dose is achieved. Once stability is confirmed, monitoring intervals can be extended based on clinical judgment. Proper administration of levothyroxine also plays a vital role in maintaining efficacy and preventing fluctuations in hormone levels. Patients should be advised to take the medication on an empty stomach, ideally 30 to 60 minutes before breakfast, and to avoid consuming any other medications, supplements, or food during that time window.. This practice enhances absorption and helps maintain consistent serum levels of the hormone.

Adverse Drug Reactions and the Importance of Monitoring in Levothyroxine Therapy

The vast majority of adverse drug reactions (ADRs) associated with levothyroxine are dose-dependent, meaning they arise primarily when the administered dose exceeds the patient's physiological requirement. These reactions often mimic the clinical features of hyperthyroidism, including symptoms such as palpitations, weight loss, anxiety, insomnia, tremors, and gastrointestinal disturbances. These effects are particularly concerning due to the involvement of critical systems, especially the cardiovascular and nervous systems, where excessive thyroid hormone activity can lead to serious complications such as atrial fibrillation, tachycardia, hypertension, and neuropsychiatric disturbances.
Given the potential severity of these manifestations, it is imperative that prompt medical evaluation and intervention be undertaken if signs of thyroid hormone excess are suspected. Timely dose adjustment or temporary cessation of therapy may be required to avoid long-term harm.

Additionally, drug-drug interactions can significantly alter levothyroxine absorption, metabolism, and efficacy, further complicating management. For example, calcium supplements, iron, antacids, certain anticonvulsants, and even some antidepressants can interfere with levothyroxine bioavailability or accelerate its clearance, leading to subtherapeutic or supratherapeutic levels. As such, comprehensive medication review and patient education are essential components of safe therapy.

To mitigate these risks and ensure therapeutic effectiveness, regular monitoring of thyroid function particularly serum TSH levels is essential. Monitoring should be performed every 6 to 8 weeks after any change in dose or formulation and periodically thereafter once a stable dose is achieved. Consistent TSH surveillance enables early detection of imbalances, allowing for timely adjustments and helping to prevent the onset of clinically significant ADRs.

In conclusion, careful dosing, awareness of potential drug interactions, and diligent monitoring are key to optimizing levothyroxine therapy while minimizing the risk of adverse outcomes.

CONCLUSION

Levothyroxine remains the gold-standard therapy for hypothyroidism and related thyroid conditions, offering effective hormonal replacement when administered correctly. However, its narrow therapeutic index and susceptibility to drug-drug and drug-food interactions demand a heightened level of clinical vigilance. This review highlights that even routine medications such as proton pump inhibitors, calcium and iron supplements, and certain antidepressants can significantly compromise LT4 absorption or alter its metabolism, leading to inadequate symptom control or iatrogenic hyperthyroidism. Equally concerning are the systemic adverse effects of levothyroxine overdose, which can manifest as cardiovascular, gastrointestinal, neuropsychiatric, and skeletal complications. From atrial fibrillation and osteoporosis

to anxiety and diarrhea, the clinical spectrum of levothyroxine related adverse reactions underscores the importance of precision in dosing and monitoring.

To ensure therapeutic success and minimize harm, clinicians must adopt a patient centered approach that includes thorough medication review, individualized dosing strategies, and consistent monitoring of thyroid function, particularly TSH and free T4 levels. Patient education on proper administration such as fasting intake and avoidance of interfering substances is crucial for maintaining hormonal stability.

With the growing complexity of polypharmacy and diverse patient needs, awareness of potential drug interactions and adverse events associated with LT4 therapy is more important than ever. By integrating pharmacological knowledge with personalized care, healthcare professionals can optimize treatment outcomes, enhance patient safety, and uphold the therapeutic promise of levothyroxine.

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