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DRUG INDUCED THYROID DISORDERS – A REVIEW

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ABSTRACT
Thyroid axis is particularly prone to interactions with wide variety of drugs and natural substances every year. These substances affect every aspect of thyroid physiology and hormone pharmacology and their interactions lead to different form of thyroid disorders majority includes hypothyroidism, thyrotoxicosis and goiter. Drugs which cause both hypothyroidism and hyperthyroidism include amiodarone, lithium and tyrosine kinase inhibitors such as sunitinib and sorafenib. The reported incidence of amiodarone induced hypothyroidism varies widely ranging from as high as 13 % in countries like UK and USA (high dietary iodine intake countries) and thyrotoxicosis 2-9.6 %. Prevalence of TKI induced hypothyroidism was 36%. Two to four months after the initiation of sorafenib, 18 % of patients were presented with hypothyroidism and 3% of patients' exhibit hyperthyroidism. In UK, the prevalence of hypothyroidism and hyperthyroidism in patients who were on lithium therapy was found to be 10.3 % and 0-1% respectively. The decision about management of drug induced thyroid dysfunctions whether to treat or not, depends on the degree of thyroid dysfunction, patient's age and in particular, on the underlying condition for which those drugs were prescribed. Clinical Pharmacist play a major role in diagnosis and management of thyroid disorders with the aim is to attenuate symptoms and also to restore normal levels of thyroid hormones and TSH for better patient care. Clinical Pharmacist can improve the health of the patients by avoiding drug induced toxicities.

KEYWORDS: Thyroid, Amiodarone, Tyrosine Kinase Inhibitors, Lithium.

INTRODUCTION
Thyroid gland is located in the neck, anterior to the trachea, between the cricoid cartilage and the suprasternal notch. Thyroid gland consists of two lobes that are connected by an isthmus. It is normally 12 to 20 g in size, highly vascular and soft in consistency. Thyroid hormone synthesis normally begins at about 11 weeks of gestation.[1]

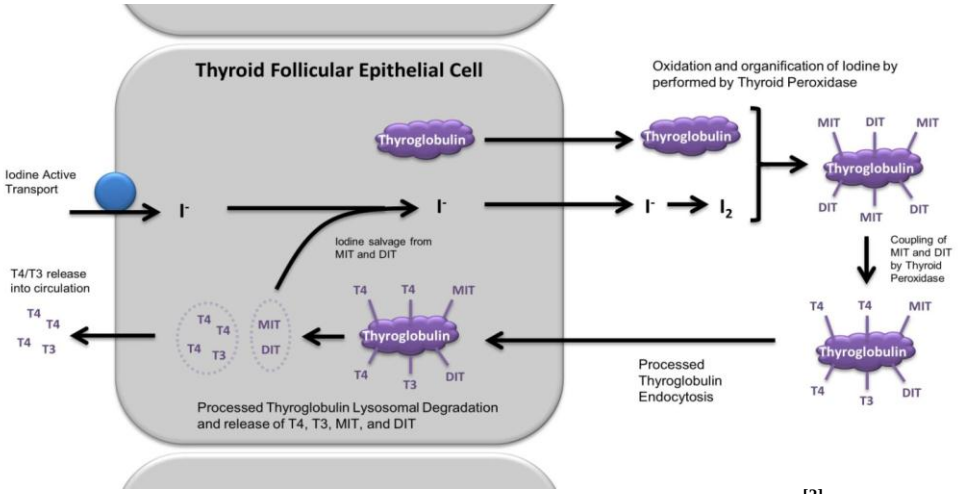

Fig 1: Formation, storage and release of thyroid hormones.[2]

T4 – Thyroxin; T3 – Triiodothyronine
MIT – Mono iodotropin; DIT – Di iodotropin

Functions of thyroid hormones

The physiologic functions of hormones can be divided into three general areas:

1. Growth and differentiations.
2. Maintenance of homeostasis.
3. Reproduction.

Thyroid hormone control about 25%of basal metabolism in most tissues. The thyroid gland produces two related hormones, thyroxine (T4) and triiodothyronine (T3). Acting through nuclear receptors, these hormones plays a critical role in cell differentiation during development and helps to maintain thermogenic and metabolic homeostasis in the adult. [1]

Drug induced thyroid disorders

Thyroid axis is particularly prone to interactions with wide variety of drugs and natural substances every year. These drugs affect every aspect of thyroid physiology and hormone pharmacology which lead to different forms of thyroid disorders such as goiter, hypothyroidism, thyrotoxicosis. [3] The mechanisms responsible for drug induced thyroid disorders can be summarized as follows:

a) Inhibition of synthesis and or release of thyroid hormones
b) Immune mechanisms
c) Drug induced thyroiditis
d) Inhibition of thyroid stimulating hormone
e) Interactions in the treatment.[3]

Drugs that causethyroid disorders are

1. Amiodarone
2. Tyrosine kinase inhibitors – sunitinib and sorafenib
3. Lithium.

1. Amiodarone

Amiodarone is highly effective drug for the prophylaxis and treatment of many cardiac arrhythmias. [4] It is a benzo furan derivative with high iodine content (39 % of its molecular weight). There is a structural similarity between amiodarone and its main metabolite desethylamiodarone (DEA) and the thyroid hormones, so the drug behaves as a partial agonist of these hormones in tissues such as the pituitary gland.

Epidemiology

The reported incidence of amiodarone induced hypothyroidism varies widely ranging from as high as 13 % in countries like UK and USA (high dietary iodine intake countries). The incidence of amiodarone induced hypothyroidism is 6 % in countries like Italy and Spain (low iodine intake countries). In western countries the prevalence of amiodarone induced hypothyroidism ranges from 5-22 % and subclinical hypothyrodism was detected about 2.5 %.The chances of occurrence of goitre was found about 20% in patients of hypothyroidism.[4] The prevalence of amiodarone induced thyrotoxicosis was 2-9.6 %. AIT is higher in males when compare to females(ratio 3:1).[2] The reported incidence of amiodarone induced thyrotoxicosis varies widely ranging from <2%-13% in countries like UK and USA.[4]

Risk factors

Hashimoto'sthyroiditis is the most common risk factor for the development and persistenceof Amiodarone induced hypothyroidism (AIH).[2] The risk was found to be high in elderly, female patients and individuals with the presence of thyroid peroxides or thyroglobulin antibodies.[4]

Pathophysiology

Amiodarone affects thyroid gland and its metabolites are unique and quite complex and occur in different mechanisms.[4]

Mechanisms include

- Inhibition hormones entry into peripheral tissues.[5]
- Inhibit the mono-deionization (type -I5 deiodinase activities) of T4. This leads to a decrease in the generation of T3 from T4, a decrease in the clearance of reverse T3 (rT3) in the thyroid gland.[5]
- Inhibition of type II 5'- deiodinase, which converts T4 to T3 in the pituitary.[5]

Amiodarone induced hypothyroidism

Hypothyroidism develops as soon as 2 weeks or as late as 39 months after the initiation of amiodarone therapy. Pathogenic mechanism of amiodarone induced hypothyroidism is that the thyroid gland is damaged by the pre- existing hashimoto's thyroiditis (auto-immune disorder) in which the antibodies directed against the thyroid gland leads to chronic inflammation. Due to chronic inflammation, synthesis of thyroid hormones decreases and leads to increase in TSH levels.[2]

Amiodarone induced thyrotoxicosis

Amiodarone induced thyrotoxicosis (AIT) may develop early or after many years of amiodarone treatment. It may be partial due to storage of drug in the thyroid tissue and their slow release into blood flow so the effect persists for long time. [5] Two types of AIT have been described. They are AIT –I and AIT-II. [2]

- Type –I AIT: Type -1 AIT usually occurs in patient with underlying thyroid pathology, such as latent Grave's disease or nodular goiter.[4]
- Type–II AIT: Type –II AIT occurs in normal thyroid glands. [2]

Clinical manifestations: Amiodarone induced hypothyroidism: Lethargy, weakness, intolerance to cold, mental sluggishness, constipation, menorrhagia, dry skin.[2]

Amiodarone induced thyrotoxicosis: Weight loss, heat tolerance, fatigue, nervousness,muscle weakness, increased frequency of stools, anxietyand palpitations.[2]

Diagnosis

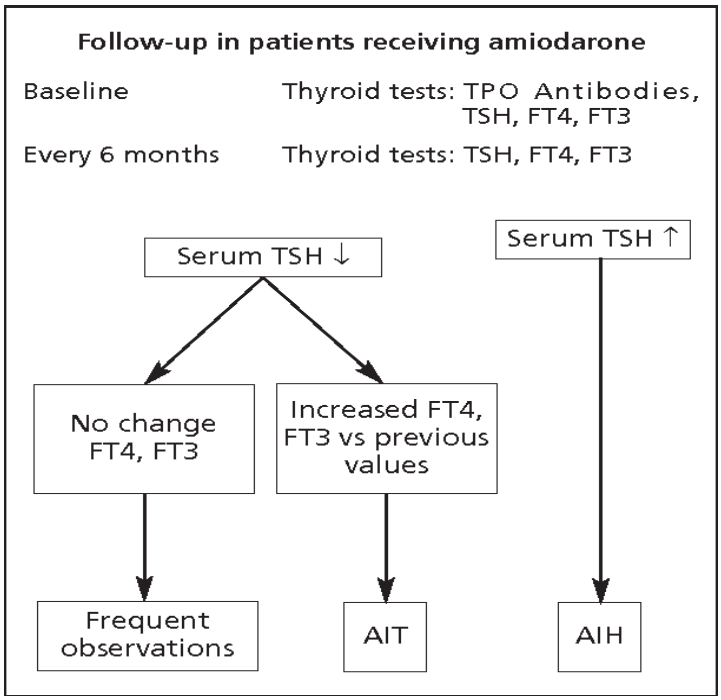

Fig 2: Monitoring thyroid function test in patients using amiodarone.[5]

Nuclear medicine and ultra sound imaging have been utilized for differentiation of AIT 1 and AIT2 or mixed forms of disease. Thyroid ultrasonography can rapidly assess thyroid volume, nodularity, parenchymal echogenicity and vascularity. Color –flow Doppler Sonography provides a non-invasive, real time assessment of thyroid vascularity.[6]

Three different traces are available including radioiodine (RAI) with ^{131}I or ^{123}I, ^{99m}pertechnetate ($^{99m}TcO4^-$) and $^{99m}TcO4^-$2-methoxy-isobutyl-isonitrile (MIBI). AIT-1 is accompanied by low, normal or even high 24-h RAI uptake; whereas the RAI uptake is mostly zero in patients with AIT 2.[6]

Table 1: Changes in thyroid function tests occurring in euthyroid amiodarone-treated subjects.[6]

Assay	Short-term therapy	Underpinning mechanism(s)	Long-term therapy	Underpinning mechanism(s)
Thyrotropin	Increased	DecreasedT4 production (Wolff-Chaikoff effect) (major contribution) Inhibition of pituitary D2 activity (minor contribution) Inhibition of T3 binding to its pituitary receptor (minor contribution)	Normal	Normalized T4 production (escape from the Wolff-Chaikoffeffect)
Thyroxine (T4): total (TT4) and free (FT4)	Increased	Inhibition of hepatic D1 activity	Slightly increased/ high normal	Inhibition of hepatic D1 activity Increased T4 production rate Decreased T4 metabolic clearance rate
Triiodothyronine: total (TT3) and free (FT3)	Decreased	Inhibition of hepatic D1 activity	Slightly decreased/ low normal	Inhibition of hepatic D1 activity Increased T4 production rate Decreased T4 metabolic clearance rate
Reverse T3	Increased	Inhibition of hepatic D1 activity	Increased	Inhibition of hepatic D1Activity
D1- type 1 iodothyronine deiodinase; D2- type 2 iodothyronine deiodinase				

Management of amiodarone-induced thyroid disease dysfunction.[2]

Amiodarone-induced hypothyroidism

Clinical hypothyroidism (TSH>10 µIU/L, FT4 low normal or decreased and clinical features of hypothyroidism).

- Treat with levothyroxine 25-50µg/ml and increase the dose until TSH is within the normal range and symptoms have resolved. Amiodarone can be continued in the majority of patients. Patient should be re-evaluated after 6-12 months of therapy to determine the continuing need for LT4 therapy.[5]
  Subclinical hypothyroidism (TSH>4.5 and 10 µIU/L and normal FT4 with absence of clinical features of hypothyroidism)
- If TPO antibody is positive, consider treating with levothyroxine. If antibody is negative and symptoms are attributable to hypothyroidism, trial of T4 and reassessed for symptomatic improvement.If asymptomatic and no antibodies, follow up at 6 weeks and 3 months thereafter.

Amiodarone-induced thyrotoxicosis (Suppressed TSH<0.1 with raised FreeT4 and FreeT3)

Management of AIT depends upon type of AIT, severity and duration of clinical features.

Type I Amiodarone induced thyrotoxicosis (AIT)

- If possible, withdraw amiodarone and patient must be treated with Carbimazole (or methimazole) 30-60 mg/day, Propylthiouracil 100-150 mg four times a day, Potassium perchlorate 0.5gm twice a day can be given to block iodide uptake
- Definitive treatment after restoration of euthyroidism is either by radioiodine or thyroidectomy.
- A Complete blood count should be done every few weeks in patients receiving thionamide and perchlorate to detect hematological alterations.[5]

Type II Amiodarone induced thyrotoxicosis (AIT)

- Prednisolone 40-60 mg/day for 2-3 months and Dexamethasone 3-6 mg.[5]Withdraw amiodarone if possible.[2]

Mixed AIT

- Patient must be treated with Carbimazole (or methimazole) 30-60 mg/day with prednisolone 40-60mg (pragmatically 40mgCarbimazole (or methimazole) and 40 mg prednisolone)
- Ifrapid response indicates type II AIT then consider stopping carbimazole (or methimazole) and poor response indicates type I AIT taper steroids and continue carbimazole (or methimazole). Consider reducing Carbimazole (or methimazole) if clinically indicated.
  Early or subclinical thyrotoxicosis (TSH 0.1-0.45 with normal FreeT4 and FreeT3 usually at lower end of reference range)
- Repeat thyroid function tests in 6 weeks, if TSH is suppressed, treat as thyrotoxicosis. If TSH is normal, follow up as normal.

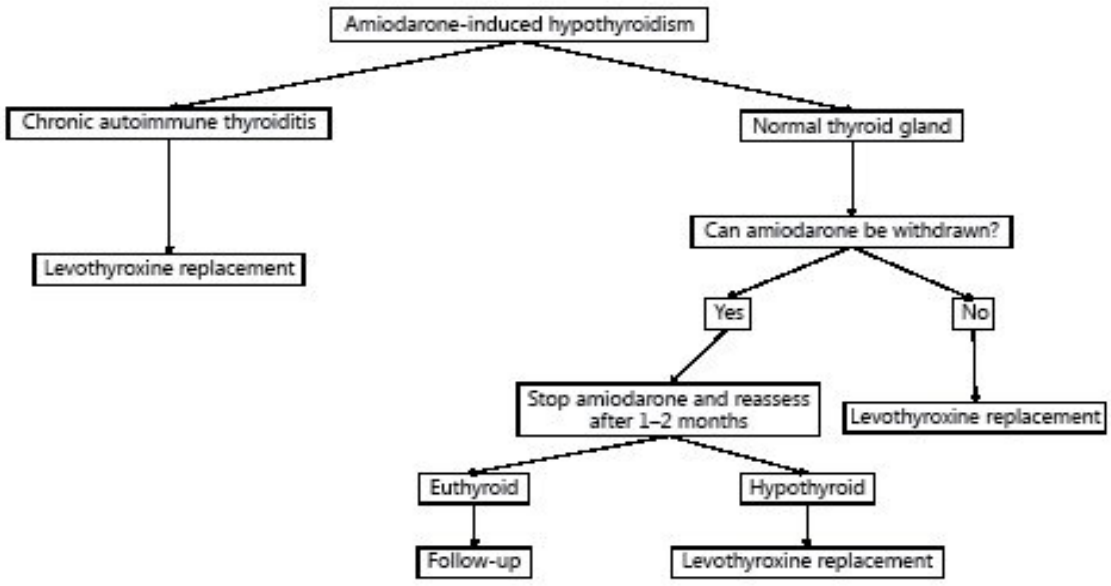

Fig. 3: Algorithm for the management of amiodarone induced hypothyoidism.[6]

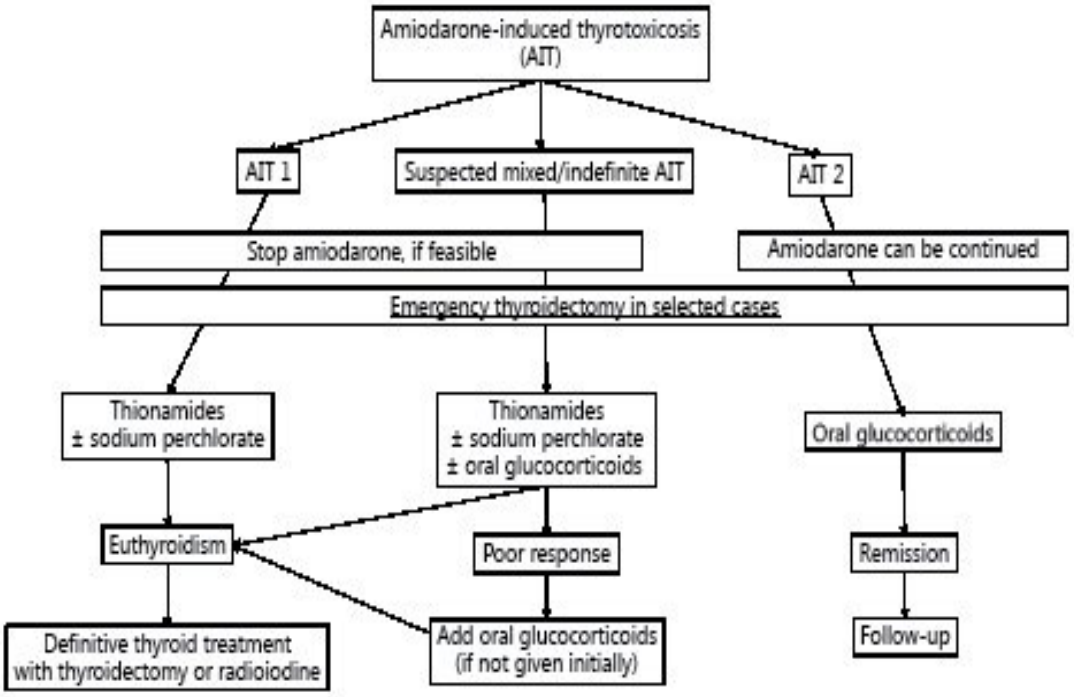

Fig. 4: Algorithm for the management of amiodarone induced thyrotoxicosis.[6]

2. Tyrosine kinase inhibitors (TKI)

Tyrosine kinases are enzymatic proteins, usually receptors. Which catalyses the transfer of phosphate from ATP totyrosine residues in peptides. They are involved in the oncogenesis through various mechanisms.[7]

Sunitinib: It is indicated for the treatment of renal cell carcinoma and stromal gastrointestinal tumors. Administration of dose is 6 weeks cycle with 4weeks of treatment (on period) followed by 2weeks of without treatment (off period).[7]

Sorafenib: It is a multitargeted TKI it interacts with VEGFRB, PDGFRB, oncogene KIT, protooncogene RET, oncogene BRAF and oncogene RAFI. It is indicated for the advanced renal cell carcinoma and hepatocellular carcinoma. It has been evaluated in lung, pancreatic, prostate cancers.[7]

Epidemiology

Sunitinib: 26 patients who received TKI's for 4-6 weeks had elevated TSH levels. Prevalence of TKI induced hypothyroidism was 36 %. Prevalence of elevated TSH levels after usage of sunitinib is 71%.[10] Prevalence of Subclinical hypothyroidism is 18 % in 39 patients.[9]

Sorafenib: 2-4 months after the initiation of sorafenib, 18% of subjects presented with hypothyroidism. 3 % of patient's exhibit hyperthyroidism.[7]

Risk factors: Age, familial history of thyroid illnesses, more than 6 cycles of treatment of tyrosine kinase inhibitors, nodular thyroid and destructive thyroiditis.[8]

Pathophysiology

Sunitinib and sorafenib are the two main tyrosine kinase inhibitors that cause thyroid disorders.[9]They act by blocking the tyrosine kinase signaling pathways that modulateoncogenesis directly or indirectly. TKI are not specific of only one Tyrosine Kinase receptors. The majority of TKI exhibit the vascular and anti- angiogenic properties by interacting with vascular endothelial growth factor (VEGP), VEGF receptors, PDGFR, RET and KIT.[7]The inhibition of angiogenesis of TKI decreases the blood flow to the thyroid gland that leads to decrease in the iodine uptake to the tyrosine follicles.[10]

Clinical manifestations

Sunitinib: Fatigue, cold tolerance, anorexia, periorbital edema, fluid retention, asthenia and alterations in skin and hair.[10]

Sofarinib: Fatigue, cold intolerance, weight gain, coarse or dry skin, periorbital and peritibial edema, bradycardia, pleural and pericardial effusions.[11]

Diagnosis

- Evaluate Thyroid function tests (TFT) includes assessment of serum TSH, T3, freethyroxin index and thyroid antibodies (antiTG, anti TPO antibodies and TSH receptor antibodies) which reveals hypothyroidism and hyperthyroidism.[10]

- Reduced thyroid volume and thyroid vascularity by Doppler ultrasound.[10]
- Assessment of ectopic thyroid tissue by ultrasonography helps in detection of destructive thyroditis.[10]
- RAIU. [10]

Management of Tyrosine Kinase Inhibitors induced thyroid dysfunction
Preexisting hypothyroidism is detected and treated before starting TKI treatment. Assessment of thyroid function on day 1 and 28 of the 6 week cycle for the first four cycles of sunitinib treatment must be done prior to the initiation of levothyroxine treatment. [19]

Patients with TSH greater than 10 µIU/L or with low free T4 levels should receive thyroid hormone replacement with levothyroxine at a dose of 1.6 µg/kg/day. In the case of coronary artery disease dose of levothyroxine should be 50 µg/day used for the first few weeks.[10]

An evaluation of the TSH concentration dosage on the first and last days of the on- period (4weeks) during the first four cycles should be done. If the TSH is normal, the measurement should then be repeated every 3 cycles. In cycle pattern it can be difficult to decide when the levothyroxine has to be introduced. The increased TSH level at the end of the off-period (2 weeks) confirms that the hypothyroidism is permanent and that it will worsen during the following cycles. Thus levothyroxine will have to be initiated. Conversely, the increased TSH levels during the ON period can be normalized at the end of OFF period and introduction of levothyroxine may lead to thyrotoxicosis.[12] Grave's disease is usually treated with antithyroid drugs i.e., methimazole.[10]

3. Lithium
Lithium is an alkali metal, which is available as lithium carbonate and lithium citrate in sustained and immediate release preparations. Lithium is an imperative drug in the long term treatment of bipolar disorders.It is also used as prophylactic treatment for the hypomania, mania, unipolar depression and other mood disorders.[14]
Risk factors: Rapid cycling of lithium, female gender, familial history of thyroid illnesses, pre-existing auto antibodies, iodine deficient diet, grave's disease, granulomatous thyroiditis.[15]

Pathophysiology
The precise mechanism by which lithium exerts its mood stabilizing effects was not still apparent. Its neurotropic effects are partially explained by the inhibition effect on the N-methyl D-aspartate receptor that mediates cellular calcium influx and suppression of activation of pro-apoptite calcium dependent signaling pathways.[14]

Mechanisms
In human, lithium administration may result in either reduced or increased thyroidal radioiodine uptake.[14] Several mechanisms are proposed to explain this dual effect among humans. Low thyroid iodine uptake could be due to lithium induced iodine retention and competition for the iodide transport within the thyroid gland. An increase in the uptake could be mediated by the increased secretion of thyroid stimulating hormone (TSH) following lithium induced hypothyroidism. Lithium inhibits synthesis and release of thyroid hormones. This inhibitory effect is due to the alteration in the tubulin polymerization and inhibition of the action of TSH on C-AMP. Lithium also alters the structure of thyroglobulin thereby affecting the iodotyroine coupling and synthesis of thyroid hormones is also affected. Inhibition of type-1 5' de-iodinase enzyme activity leads to inhibition in the conversion of T4 to T3.[14]

Clinical manifestations: Tiredness, poor ability to tolerate cold, weight gain, fatigue, constipation, weakness, depressed mood, decreased concentration.[16]

Epidemiology
Among 330 manic depression patients on lithium therapy, goiter was found to be in 12 patients and the prevalence was 3.6 %. [14] Among 96 patients with affective disorders in Germany, goiter was reported in 53 patients [55 %] who were on lithium therapy. Hypothyroidism and subclinical hypothyroidism with / without concomitant goiter is also prevalent among the patient on lithium therapy ranging from 0 % to 53 %. In UK, the prevalence of hypothyroidism and hyperthyroidism in lithium treated patients was found to be 10.3 % and 0-1% respectively.[17] Long-term therapy of lithium causes thyrotoxicosis.2 of 111men who are using lithium for 80 days developed thyrotoxicosis. The incidence rate in men was 2.7 %. 6 of 152 female patients who were using lithium for long period developed thyrotoxicosis and the incidence rate was 6.4 %.[14]

Diagnosis
- Assessment of Thyroid Function Test (TFT)prior to starting lithium prophylaxis should include measurement of serum concentration of TSH, FT3,FT4, anti thyroperoxidase antibodies (AbTPO) and ultrasonic scanning.[18]
- Measurement of AbTPO and ultrasonic scanning may be repeated at 2-3 years ofinterval.[18]
- Thyroid ultrasonography has been demonstrated to be a simple, cheap and sensitive method for screening of goiter and thyroid abnormalities among patient with lithium therapy.[17]
- Thyroid biopsy shows the evidence of autoimmune thyroiditis due to lithium treatment.[17]

Management of lithium induced hypothyroidism
Clinical hypothyroidism: If a good response is achieved and the patient is willing to continue with lithium, the hypothyroidism may be treated with thyroxine that will maintain normal serum TSH levels.[16]If the patient develops affective symptoms of hypothyroidism and/or the TFTs do not normalize, thyroid supplementation is

appropriate. Lithium cessation will result in reversal of the abnormalities, usually within 1-2 months. If a patient on thyroxine is stopping lithium, thyroxine should be gradually tapered off over a month and the TFTs measured monthly until they return to normal. [16]

Table 2: Subclinical hypothyroidism: Serum TSH levels and suggested management.

Serum TSH Levels	Intervention
5-10 µIU/L&patient asymptomatic	• Thyroid supplementation not immediately necessary. • Repeat TSH levels preferably after month (at least 2 weeks but not more than 2 months). • If TSH remain elevated monitor closely (every 3 months) for symptom exacerbations or progression to overt hypothyroidism.
5-10 µIU/L& patient reports symptoms related to hypothyroidism	• Initiate thyroxine therapy(25-50mcg) • Baseline neurocognitive assessment may be useful to serve as baseline in future for those with cognitive therapy.
>10 µIU/L	• Initiate thyroxine therapy regardless of whether patient symptomatic. • These patients are at high risk for progression to overt hypothyroidism.

Management of Lithium induced Hyperthyroidism

Cases of hyperthyroidism associated with lithium treatment are less common compared to hypothyroidism and goiter.[18]Lithium treatment must not be stopped or the dose modified unless the serum levels is beyond the therapeutic range.[18] Once lithium is discontinued and amanic attack is reoccurred, it must be treated with haloperidol and radioiodine followed by carbimazole.[19]

- Lithium induced hyperthyroidism should betreated with antithyroid drugs such as carbimazole with /without steroids.[14]
- Radioiodine or thyroidectomy should be reserved for patients with lithium induced grave's disease especially in cases of poor compliance to antithyroid drugs.[14]
- In case of toxic nodular goiter with or without compressive symptoms, a thyroidectomy is indicated.[14]

ROLE OF CLINICAL PHARMACIST

Clinical Pharmacist plays a vital role in management of thyroid disorders. Clinical pharmacist, with his knowledge and experience can help in early detection and proper management of disease. With his skills in areas such as ADR management, Patient counselling, Drug interactions and life style modification suggestions, Clinical Pharmacist can improve the health of the patients by avoiding drug induced toxicities.

ABBREVIATIONS

TKI- Tyrosine kinase inhibitors
PDGFR- Platelet Derived Growth Factor Receptors
TSH- Thyroid Stimulating Hormone
TPO- Tyro peroxidase.

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