International Journal of Pharmaceutical Research and Applications
Volume 8, Issue 6 Nov-Dec 2023, pp: 809-821www.ijprajournal.com ISSN: 2249-7781

Practice School Report Of "Pharmacovigilance"

Mr. Dattatray Sudhakar Tuwar*,Assistant Prof.Tuwar Ajit.B,Dr.Megha Salve

(B. PHARMACY, SEM VII)
Shivajirao pawar college of pharmacy pachegoan.413725
Dr. Babasaheb Ambedkar Technological University, Lonere

Submitted: 20-11-2023 Accepted: 30-11-2023

ACKNOWLEDGEMENTS

Working On This Domain '**PHARMACOVIGILANCE**' was A Source Of Immense Knowledge To Me. I Am Thankful For Their Aspiring Guidance. First Of All, I Would Like To Thank Mr.Tuwar Sir For Allowing Me To Be A Part Of This Activity And Exposing Myself To The Field Of Pharmacology And Pharmacovigilance Mr.Tuwar.A.B. Sir Has Guided Me Throughout These Processes And I Am Very Thankful For This. I Learn About The Different Pharmacological Clinical For Drugs , Basic Concepts In Pharmacovigilance , How To Report ADR And Giving Me Great Ideas On How To Approach My Knowledge. He Was Always Willing To Edit My Presentations And Report Always Providing Positive Feedback To Improve My Skills. I Am Very Grateful For The Opportunity He Has Given Me. He Was Always Giving Me A Positive Approach To The Particular Ideas And Also For How To Work On Them. His Dynamism Vision Sincerity And Motivation Have Deeply Inspired Me. It Was A Great Privilege And Honor To Work And Study Under This Guidance. I Was Able To Learn Much About The Process Of Research And How To Conduct My Literature Survey.

Also A Big Thanks To Everyone Else In The Pharmacology Department and pharmaceutics department, It Was A Pleasure Working With Everyone Shouts Out To My Friends Who Helped Me With Practical Data. Big Thanks ToDr.Megha Salve Mam (Principal, Shivajirao Pawar College Of Pharmacy) For Selecting Me For This Wonderful Domain. I Would Also Like To ThanksTo The All Faculty Members Of Shivajirao Pawar College Of Pharmacy For Playing An Inspiring And Supportive Role In This Activity.
Special Thanks To All The Doctor , Paramedical Staff Of Shirsath Hospital , Shrirampur . For Guided Me Regarding ADR Of Selected Drug.

Module 1 :- Clinical Research.

1)Defination And Phases Of Clinical Trial:- Clinical trial is a prospective ethically designed Investigation in human subjects to objectively Discover/verify/compare the results of Two or More therapeutic measure(drugs).When a compound deserving trial in man is Identified by animal studies, the regulatory Authorities a re approached who on satisfaction issue an ' investigational new drug' (IND) License.

- **Phase I – Human Pharmacology And Safety.**

The first human administration of the drug is carried out by qualified clinical pharmacologists/trained physicians in a setting where all vital functions are monitored and emergency/ resuscitative facilities are available .
The human pharmacokinetic parameters Of the drug a re measured for the first time. No blinding is done the study is open label.

- **Phase O :- Micro Dosing Study.**

This is a new strategy being developed to reduce the cost and time of the drug development process.This has Alarmed the FDA (USA) and the European Medicines Agency to encourage novel cost-culling approaches in Drug development. One such tool is the microdosing Human study undertaken before phase- I trial, and is Also called phase "O" Study.

- **Phase II :- Therapeutic Exploration And Dose Ranging.**

This is conducted by physicians who are trained as clinical investigators, and involve 100-500 patients selected according to specific inclusion and exclusion criteria.

The primary Aim is establishment of therapeutic efficacy, Dose range and ceiling effect

International Journal of Pharmaceutical Research and Applications
Volume 8, Issue 6 Nov-Dec 2023, pp: 809-821www.ijprajournal.com ISSN: 2249-7781

in a controlled Setting. Tolerability and pharmacokinetics are Studied as extension of phase I. The study is Mostly controlled and randomized, and may be Blinded or open label.

➢ **Phase III:- Therapeutic Confirmation/ Comparison:-**

Generally these are randomized double blind comparative trials conducted on a larger patient population (500- 3000) by several physicians (usually specialists in treating the target disease) at many centres.

The aim is to establish the value of the drug in relation to existing therapy.

A ·new drug application' (DA) is submitted To the licencing authority (like FDA), who if Convinced give marketing permission.

➢ **Phase IV :- Postmarketing Surveillance / Data Gathering Studies.**

InAfter the drug has been marketed for general use. practicing physicians are identified through whom data are collected on a structured proforma about the efficacy, acceptability and adverse effects of the drug in the real field situation.

Further therapeutic trials involving special groups like children, elderly, pregnant/lactating women. patients with renal/hepatic disease, etc. (which are generally excluded during clinical trials) may be unde11aken at this stage.

2)Function Of Drug Controller General Of India (DCGI) And Central Drug Standard Control Organization (CDSCO).

➢ **Function Of Drug Controller General Of India (DCGI).**

- Lay Down The Standard And Quality of Manufacturing, Selling, Import And Distribution Of Drug In India.
- Preparation And Maintenance Of National Reference Standard.
- To bring About The Uniformity In The Enforcement Of The Drug And Cosmetic Act

➢ **Function Of Central Drug Standard Control Organization (CDSCO).**

- Approval of new drugs and clinical trials.
- Import Registration and Licensing
- Licensing of Blood banks, LVPS, Vaccines, Pie-DNA products and some medical devices and diagnostic agents.
- Amendment to D and C Act and Rules.
- Banning of drugs and cosmetics.
- Grant to Test license, Personal License, NOC'S for export.
- Testing of drugs by Central Labs.
- Publication of Indian Pharmacopoeia.
- Monitoring adverse drug reactions.
- Guidance on technical matter.

3)Types Of Regulatory Applications.

- **Investigational New Drug (IND):-**

An IND, or investigational new drug application,is a submission to the U.S. Food and Drug Administration (FDA) requesting permission to initiate a clinical study of a new drug product in the United States.

- **New Drug Application :-**

The vehicle through which drug sponsors formally propose that the regulatory body Approves a new pharmaceutical for sale and marketing, and the data gathered during the Animal studies and human clinical trials of an investigational new product becomes a part of NDA.

- **Aim Of NDA:-**

Safety and effectiveness of drug, Benefits overweigh risks, Is the drug's proposed labeling (package insert) appropriate, and what should it contain.

- **Abbreviated New Drug Application (ANDA):-**

ANDAs are used when a patent has expired on a product that has been in the U.S.market and a company wishes to market a copy. In the United States, a drug patentis for 20 years. Subsequently, a manufacturer is able to submit an abbreviated application for that product, provided that it certifies that the product patent in question has already expired, is invalid, or will not be infringed.

Module 2:- Good Clinical Practice

1)Objectives and scope of "ICH-Good Clinical Practice" and "New Drugs and Clinical Trial Rules 2019"

➢ **Objectives And Scope Of "ICH – Good Clinical Practice"**

- Good Clinical Practice (GCP) is an international ethical and scientific quality standard for designing, conducting, recording and reporting trials that involve the participation of human subjects.
- Compliance with this standard provides public assurance that the rights, safety and well-being

International Journal of Pharmaceutical Research and Applications
Volume 8, Issue 6 Nov-Dec 2023, pp: 809-821www.ijprajournal.com ISSN: 2249-7781

of trial subjects are protected, consistent with the principles that have their origin in the Declaration of Helsinki, and that the clinical trial data are credible.

- The objective of this ICH GCP Guideline is to provide a unified standard for the European Union (EU), Japan and the United States to facilitate the mutual acceptance of clinical data by the regulatory authorities in these jurisdictions.
- The guideline was developed with consideration of the current good clinical practices of the European Union, Japan, and the United States, as well as those of Australia, Canada, the Nordic countries and the World Health Organization (WHO).

➢ **New Drugs and Clinical Trial Rules 2019.**

- The New drugs and Clinical trials rules 2019 (New rules) was introduced on 19th March 2019 by Government of India. New rules have set specific requirements for ethics committee (EC).
- The EC is required to follow requirements set as per New rules and to forward their report to Central Licensing Authority (CLA).
- This document is divided into different sections like definitions and applicable chapter & schedules for EC; changes related to registration of clinical studies and biomedical and health research; changes related to constitution, functions, proceedings, responsibility of EC for clinical trial; maintenance of records by EC; suspension and cancellation of registration of EC, post-trial access of drugs, changes and clarity related to academic clinical trials and role of ECs in compensation and medical management process.

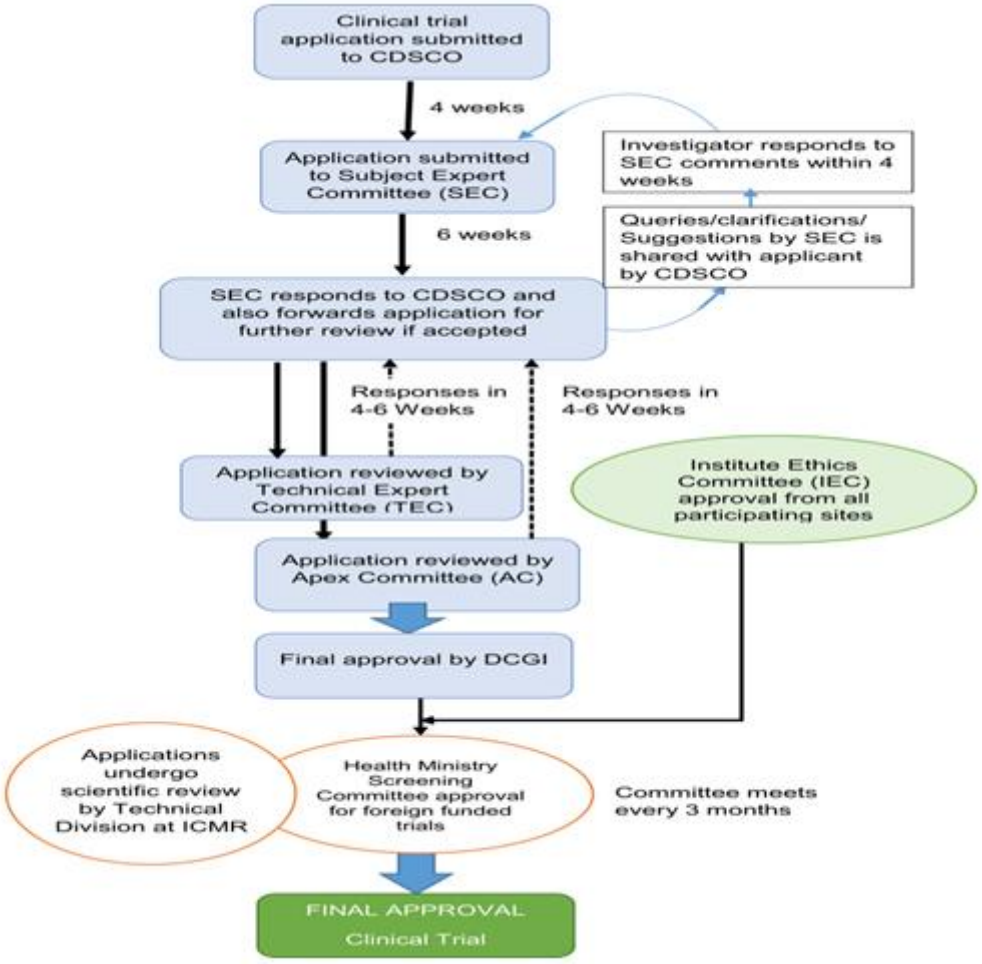
2) Protocol Designing For Clinical Trial:-

A research protocol is a document that describes the background, rationale, objectives, design, methodology, statistical considerations, and organization of a clinical research project. According to the ICH Good Clinical Practice guidelines, a protocol should include the following topics:

- Title Page (General Information)
- Background Information
- Objectives/Purpose
- Study Design
- Selection and Exclusion of Subjects
- Treatment of Subjects
- Assessment of Efficacy
- Assessment of Safety
- Adverse Events
- Discontinuation of the Study
- Statistics
- Quality Control and Assurance
- Ethics
- Data handling and Recordkeeping
- Publication Policy
- Project Timetable/Flowchart
- References
- Supplements/Appendices

3) Process Of Clinical Trial Application.

International Journal of Pharmaceutical Research and Applications
Volume 8, Issue 6 Nov-Dec 2023, pp: 809-821www.ijprajournal.com ISSN: 2249-7781



Module 3:-Concept Of Pharmacovigilance

1. Definition, objectives, types and components of pharmacovigilance.

- **Definition :-**

Pharmacovigilance (PV, or PhV), also known as drug safety, is the pharmacological science relating to the collection, detection, assessment, monitoring, and prevention of adverse effects with pharmaceutical products.

The etymological roots for the word "pharmacovigilance" are: pharmakon (Greek for drug) and vigilare (Latin for to keep watch).

- **Objectives:-**

- Improve patient care and safety in relation to the use of medicines and all medical and paramedical interventions.
- Improve public health and safety in relation to the use of medicines.
- Detect problems related to the use of medicines and communicate the findings in a timely manner;
- Contribute to the assessment of benefit, harm, effectiveness and risk of medicines, leading to the prevention of harm and maximization of benefit;
- Encourage the safe, rational and more effective (including cost-effective) use of medicines; and pharmacovigilance 22 pharmacovigilance

- **Components of pharmacovigilance.**

- Case-control study (Retrospective study).
- Prospective study (Cohort study).
- Population statistics.
- Intensive event report.
- The spontaneous report in the case is the population of the single case report.

International Journal of Pharmaceutical Research and Applications
Volume 8, Issue 6 Nov-Dec 2023, pp: 809-821www.ijprajournal.com ISSN: 2249-7781

2.Constitutionand objectives of Pharmacovigilance Program of India (PvPI).

- To monitor Adverse Drug Reactions (ADRs) in Indian population.
- To create awareness amongst health care professionals about the importance of ADR reporting in India.
- To monitor benefit-risk profile of medicines.
- Generate independent, evidence based recommendations on the safety of medicines.
- Support the CDSCO for formulating safety related regulatory decisions for medicines.
- Communicate findings with all key stakeholders.
- Create a national centre of excellence at par with global drug safety monitoring standards.

3.List of National Adverse Drug Monitoring Centers (AMCs) and their functions

Sr.No	Address	Coordinators
1	Department of Pharmacology, All India Institute of Medical Sciences, New Delhi.	Dr. Y.K. Gupta National Coordinator
1.	Department of Pharmacology, &nbs &nbsbsp; The rapeutics & Toxicology, Govt. Medical College, Bakshi Nagar, Jammu.	Dr. Vishal Tandon
2.	Department of Pharmacology, PGIMER, Chandigarh	Dr. Bikash Medhi
3.	Department of Pharmacology, R.G. Kar Medical College, Kolkatta	Dr. Anjan Adhikari
4.	Department of Pharmacology, Lady Hardinge Medical College, New Delhi	Dr. H.S. Rehan
5.	Department of Clinical Pharmacology, Seth GS Medical College & KEM Hospital, Parel, Mumbai	Dr. Urmila Thatte
6.	Department of Clinical & Experimental Pharmacology, School of Tropical Medicine, Chittaranjan Avenue, Kolkata	Dr. Santanu Tripathi
7.	Department of Pharmacology, JIPMER, Pondicherry	Dr. C Adithan
8.	Department of Clinical Pharmacy, JSS Medical College Hospital , Karnataka	Dr. Parthasarathi G
9.	Department of Pharmacology , Medical College , Guwahati. Assam	Dr. Mangala Lahkar
10.	Institute of Pharmacology , Madras Medical College, Chennai	Dr. R Nandini
11.	Department of Pharmacology, SAIMS Medical College , Indore-Ujjain	Dr. Chhaya goyal
12.	Department of Pharmacology, GSVM Medical College, Swaroop Nagar, Kanpur, U.P.	Dr SP Singh
13.	Department of Pharmacology, Pandit Bhagwat Dayal Sharma, Post Graduate Institute of Medical Sciences, Rohtak, Haryana.	Dr MC Gupta
14.	Department of Pharmacology, Dayanand Medical College and Hospital, Ludhiana, Punjab	Dr. Sandeep Kaushal
15.	Department of Clinical Pharmacology,	Dr. ZA Wafai

International Journal of Pharmaceutical Research and Applications
Volume 8, Issue 6 Nov-Dec 2023, pp: 809-821www.ijprajournal.com ISSN: 2249-7781

	Sher-i-Kashmir Institute of Medical Sciences, Srinagar, J&K.	
16.	Himalayan Institute of Medical Sciences, Dehradun, Uttrakhand	Dr. DC Dhasmana
17.	Department of Pharmacology, Santosh Medical University, Santosh Nagar, Ghaziabad	Dr VC Chopra
18.	Department of Pharmacology, SMS Medical College , Jaipur	Dr. Mukul Mathur
19.	Department of Clinical Pharmacology, Christian Medical College,Vellore, Tamil Nadu	Dr. Sujith chandy

❖ **Function :-**

- To analyze the benefit-risk ratio of marketed medications.
- To generate evidence based information on safety of medicines.
- To support regulatory agencies in the decision-making process on use of medications.
- To communicate the safety information on use of medicines to various stakeholders ton prevent/ minimize the risk.

Module 4 :- International Conference on Harmonization (ICH) E2e Guidelines.

1. Elements of the non-clinical and clinical safety specification.

Non Clinical :- Within the Specification, this section should present non-clinical safety findings that have not been adequately addressed by clinical data, for example:

- Toxicity (including repeat-dose toxicity, reproductive/developmental toxicity, nephrotoxicity, hepatotoxicity, genotoxicity, carcinogenicity etc.);
- General pharmacology (cardiovascular, including QT interval prolongation; nervous system; etc.);
- Drug interactions;
- Other toxicity-related information or data. If the product is intended for use in special populations, consideration should be given to whether specific non-clinical data needs exist.

Clinical :-

a) Limitation of the human safety database:-

Limitations of the safety database (e.g., related to the size of the study population, study inclusion/exclusion criteria) should be considered, and the implications of such limitations with respect to predicting the safety of the product in the marketplace should be explicitly discussed. Particular reference should be made to populations likely to be exposed during the intended or expected use of the product in medical practice.

The world-wide experience should be briefly discussed, including:

• The extent of the world-wide exposure;
• Any new or different safety issues identified;
• Any regulatory actions related to safety.

b)Populations not Studied in the Pre-Approval Phase:-

The Specification should discuss which populations have not been studied or have only been studied to a limited degree in the pre-approval phase. The implications of this with respect to predicting the safety of the product in the marketplace should be explicitly discussed (CTD 2.5.5). Populations to be considered should include (but might not be limited to):-

- Children;
- The elderly;
- Pregnant or lactating women;
- Patients with relevant co-morbidity such as hepatic or renal disorders;
- Patients with disease severity different from that studied in clinical trials;
- Sub-populations carrying known and relevant genetic polymorphism;
- Patients of different racial and/or ethnic origins.

2.Identification and evaluation of risks including drug-drug interactions and drug-food interactions.

Identified and potential pharmacokinetic and pharmacodynamic interactions should be discussed. For each, the evidence supporting the interaction and possible mechanism should be summarized, and the potential health risks posed for the different indications and in the different populations should be discussed.

International Journal of Pharmaceutical Research and Applications
Volume 8, Issue 6 Nov-Dec 2023, pp: 809-821www.ijprajournal.com ISSN: 2249-7781

3. Design and conduct of observational studies.

Carefully designed and conducted pharmacoepidemiological studies, specifically observational (non-interventional, non-experimental) studies, are important tools in pharmacovigilance. In observational studies, the investigator "observes and evaluates results of ongoing medical care without 'controlling' the therapy beyond normal medical practice."

Before the observational study that is part of a Pharmacovigilance Plan commences, a protocol should be finalised. Experts from relevant disciplines (e.g., pharmacovigilance experts, pharmacoepidemiologists and biostatisticians) should be consulted. It is recommended that the protocol be discussed with the regulatory authorities before the study starts.

It is also suggested that the circumstances in which a study should be terminated early be discussed with regulatory authorities and documented in advance. A study report after completion, and interim reports if appropriate, should be submitted to the authorities according to the milestones within the Pharmacovigilance Plan. Study protocols should, as a minimum, include the study aims and objectives, the methods to be used, and the plan for analysis.

The final study report should accurately and completely present the study objectives, methods, results, and the principal investigator's interpretation of the findings. It is recommended that the sponsor follow good epidemiological practice for observational studies and also internationally accepted guidelines, such as the guidelines endorsed by the International Society for Pharmacoepidemiology.

In some of the ICH regions, local laws and guidelines also apply to the design and conduct of observational studies and should be followed.

Module 5: Selection of Drug Class

1. **Selection of a drug class for pharmacovigilance study using different criteria :-**

- **Drug Class :- Levothyroxine (Harmone)**
- **Commercial availability:-**Levothyroxine drugs include Abbott's Synthoid also Eltroxin, Euthyrox, Levo-T, Levothroid, Levoxyl, Np Thyroid, , Thyquidity, Tirosint, Unithroid .During a mean follow-up of 6 years, 25,954 (5.2%) hypothyroid patients and 59,105 (3.9%) controls died. Hypothyroidism was significantly associated with increased all-cause mortality (adjusted hazard ratio [HR], 1.14; 95% confidence interval [CI] 1.12–1.16) even with levothyroxine treatment. When stratified by age, sex, and cardiovascular disease risk, independent associations between hypothyroidism and mortality remained significant in all subgroups. The risk of mortality was higher in the < 65 age group (HR: 1.25, 95% CI: 1.22–1.29), men (HR: 1.28, 95% CI: 1.25–1.31), and the high cardiovascular disease risk group (HR: 1.31, 95% CI: 1.29–1.34). The mortality rate of hypothyroid patients was highest within 1 year of treatment and decreased with time.

2.Profiling of selected drug class.

- **Mechanism Of Action :-**Levothyroxine is a synthetically prepared levo-isomer of the thyroid hormone thyroxine (T4, a tetra-iodinated tyrosine derivative) that acts as a replacement in deficiency syndromes such as hypothyroidism. T4 is the major hormone secreted from the thyroid gland and is chemically identical to the naturally secreted T4: it increases metabolic rate, decreases thyroid-stimulating hormone (TSH) production from the anterior lobe of the pituitary gland, and, in peripheral tissues, is converted to T3. Thyroxine is released from its precursor protein thyroglobulin through proteolysis and secreted into the blood where is it then peripherally deiodinated to form triiodothyronine (T3) which exerts a broad spectrum of stimulatory effects on cell metabolism. T4 and T3 have a relative potency of ~1:4.
- Thyroid hormone increases the metabolic rate of cells of all tissues in the body. In the fetus and newborn, thyroid hormone is important for the growth and development of all tissues including bones and the brain. In adults, thyroid hormone helps to maintain brain function, food metabolism, and body temperature, among other effects. The symptoms of thyroid deficiency relieved by levothyroxine include slow speech, lack of energy, weight gain, hair loss, dry thick skin and unusual sensitivity to cold.
- The thyroid hormones have been shown to exert both genomic and non-genomic effects.9 They exert their genomic effects by diffusing into the cell nucleus and binding to thyroid hormone receptors in DNA regions called thyroid hormone response elements (TREs) near genes.2 This complex of T4, T3, DNA,

International Journal of Pharmaceutical Research and Applications
Volume 8, Issue 6 Nov-Dec 2023, pp: 809-821www.ijprajournal.com ISSN: 2249-7781

and other coregulatory proteins causes a conformational change and a resulting shift in transcriptional regulation of nearby genes, synthesis of messenger RNA, and cytoplasmic protein production.2,6 For example, in cardiac tissues T3 has been shown to regulate the genes for α- and β-myosin heavy chains, production of the sarcoplasmic reticulum proteins calcium-activated ATPase (Ca2+-ATPase) and phospholamban, β-adrenergic receptors, guanine-nucleotide regulatory proteins, and adenylyl cyclase types V and VI as well as several plasma-membrane ion transporters, such as Na+/K+–ATPase, Na+/Ca2+ exchanger, and voltage-gated potassium channels, including Kv1.5, Kv4.2, and Kv4.3. 7 As a result, many cardiac functions including heart rate, cardiac output, and systemic vascular resistance are closely linked to thyroid status.

- The non-genomic actions of the thyroid hormones have been shown to occur through binding to a plasma membrane receptor integrin aVb3 at the Arg-Gly-Asp recognition site.12 From the cell-surface, T4 binding to integrin results in down-stream effects including activation of mitogen-activated protein kinase (MAPK; ERK1/2) and causes subsequent effects on cellular/nuclear events including angiogenesis and tumor cell proliferation.
- **Pharmacological Effects :-** Oral levothyroxine is a synthetic hormone that exerts the same physiologic effect as endogenous T4, thereby maintaining normal T4 levels when a deficiency is present.
- Levothyroxine has a narrow therapeutic index and is titrated to maintain a euthyroid state with TSH (thyroid stimulating hormone) within a therapeutic range of 0.4–4.0 mIU/L.10 Over- or under-treatment with levothyroxine may have negative effects on growth and development, cardiovascular function, bone metabolism, reproductive function, cognitive function, emotional state, gastrointestinal function and glucose and lipid metabolism. The dose of levothyroxine should be titrated slowly and carefully and patients should be monitored for their response to titration to avoid these effects. TSH levels should be monitored at least yearly to avoid over-treating with levothyroxine which can result in hyperthyroidism (TSH <0.1mIU/L) and symptoms of increased heart rate, diarrhea, tremor, hypercalcemia, and weakness to name a few.
- As many cardiac functions including heart rate, cardiac output, and systemic vascular resistance are closely linked to thyroid status,7 over-treatment with levothyroxine may result in increases in heart rate, cardiac wall thickness, and cardiac contractility and may precipitate angina or arrhythmias, particularly in patients with cardiovascular disease and in elderly patients. In populations with any cardiac concerns, levothyroxine should be initiated at lower doses than those recommended in younger individuals or in patients without cardiac disease. Patients receiving concomitant levothyroxine and sympathomimetic agents should be monitored for signs and symptoms of coronary insufficiency. If cardiac symptoms develop or worsen, reduce the levothyroxine dose or withhold for one week and restart at a lower dose.
- Increased bone resorption and decreased bone mineral density may occur as a result of levothyroxine over-replacement, particularly in post-menopausal women. The increased bone resorption may be associated with increased serum levels and urinary excretion of calcium and phosphorous, elevations in bone alkaline phosphatase and suppressed serum parathyroid hormone levels. Administer the minimum dose of levothyroxine that achieves the desired clinical and biochemical response to mitigate this risk.
- Addition of levothyroxine therapy in patients with diabetes mellitus may worsen glycemic control and result in increased antidiabetic agent or insulin requirements. Carefully monitor glycemic control after starting, changing or discontinuing levothyroxine.
- **Indications :-** Levothyroxine is indicated as replacement therapy in primary (thyroidal), secondary (pituitary) and tertiary (hypothalamic) congenital or acquired hypothyroidism. It is also indicated as an adjunct to surgery and radioiodine therapy in the management of thyrotropin-dependent well-differentiated thyroid cancer.

Adverse Effects:-

- Chest pain, discomfort, or tightness
- decreased urine output
- difficult or labored breathing
- difficulty with swallowing

International Journal of Pharmaceutical Research and Applications
Volume 8, Issue 6 Nov-Dec 2023, pp: 809-821www.ijprajournal.com ISSN: 2249-7781

- dilated neck veins
- extreme fatigue
- fainting
- fast, slow, irregular, pounding, or racing heartbeat or pulse
- fever
- heat intolerance
- hives or welts, skin itching, rash, or redness
- irregular breathing
- irritability
- menstrual changes
- nausea
- pain or discomfort in the arms, jaw, back, or neck
- sweating
- swelling of the eyes, face, lips, throat, or tongue
- tremors
- Rare
- Blurred or double vision
- dizziness
- eye pain
- lack or slowing of normal growth in children
- limp or walk favoring one leg
- pain in the hip or knee
- seizures

- **Drug Interaction :-**
- **Antacids :-**Most antacids, such as Tums, have calcium, aluminum, or magnesium in them. They're usually used to treat heartburn. These substances form a bond with levothyroxine, causing it to be less absorbed. Levothyroxine should be taken at least 4 hours apart from these medications**.**
- **Bile acid sequestrants:-**This class of cholesterol-lowering medications includes colesevelam (Welchol), cholestyramine (Prevalite), and colestipol (Colestid). These medications can lower the absorption of levothyroxine. It's recommended to take them at least 4 hours before levothyroxine.
- **Ion exchange resins:-**This class of medications includes sodium polystyrene sulfonate and sevelamer (Renvela). They can help lower potassium and phosphorus levels in your body, respectively. These medications can lower the absorption of levothyroxine. It's recommended to take them at least 4 hours before levothyroxine.
- **Proton pump inhibitors (PPIs):-**This class of heartburn and GERD medications includes omeprazole, pantoprazole (Protonix), and esomeprazole (Nexium). Since these medications lower the acidity of the stomach, they can lower the absorption of levothyroxine.
- **Phenobarbital :-**This antiseizure medication causes faster breakdown of levothyroxine in the body. This means a higher dose of levothyroxine may be needed.
- **Rifampin:-**This antibiotic medication causes faster breakdown of levothyroxine in the body. This means a higher dose of levothyroxine may be needed.
- **Amiodarone** (**Pacerone**):- This medication can cause slightly higher T4 (inactive thyroid hormone) levels by affecting conversion of levothyroxine to its active form.
- **Beta blockers:-**This class includes medications like propranolol. These medications can change thyroid levels, but usually the effects normalize and no changes are necessary. This potential interaction is mostly relevant for high doses of propranolol.
- **Contraindications :-**
- Acute myocarditis, pancarditis
- Active cardiac arrhythmias
- Thyrotoxicosis
- Hyperthyroidism

Module 6: Selection of Drug.

- **Drug:-** Thyroxin Sodium**.**
- **Class**:-. Levothyroxine.
- **Chemical Formula**:- C15-H13-I4-NNaO5
- **Molecular weight**:- 798.85 g/mol.
- **Chemical Name.:-** sodium 4-{4-[(2S)-2-amino-2-carboxyethyl]-2,6- diiodophenoxy}-2,6-diiodobenzen-1-olate
- **Synonyms**:-
- L-THYROXIN SODIUM
- Sodium levothyroxine
- SODIUM LEVOTHYROXINE
- L-THYROXINE SODIUM SALT
- L-THYROXINE SODIUM, HYDRATE
- SODIUM LEVOTHYROXINE, HYDRATE
- L-Thyroxine sodium salt hydrate
- L-THYROXINE SODIUM SALT, HYDRATE
- 3-[4-4-HYDROXY-3,5-DIIODOPHENOXY-3,5-DIIODOPHENYL]-L-ALANINE, HYDRATE

- **Brand Name**:-
- **India** :-
- Synox | Thyrosec (100mcg) | Thyronorm (150 mcg) | Thyronorm (125mcg) | Thyroking |

International Journal of Pharmaceutical Research and Applications
Volume 8, Issue 6 Nov-Dec 2023, pp: 809-821www.ijprajournal.com ISSN: 2249-7781

Eltroxin (100 mcg) | Thyronorm | Thyrowin | Thyronorm (50 mcg) | Thyrosec (50 mcg)

- **International** :-
- Synthroid, Thyrax, Euthyrox, Levoxyl, Levothroid, Levaxin, L-Thyroxine, Eltroxin, Thyrox

Module 7: Identification of Adverse Effects of a Selected Drug

❖ **Very common (affects more than 1 in 10 people**)
- increased appetite
- weight loss
- heat sensitivity
- excessive sweating
- headache
- hyperactivity
- nervousness
- anxiety

❖ **Common (affects less than 1 in 10 people)**
- irritability
- mood swings
- trouble sleeping
- tiredness
- tremors
- muscle weakness

❖ **Uncommon (affects less than 1 in 100 people)**
- changes in menstrual periods
- hair loss (usually temporary)

❖ **Very rare (affects less than 1 in 10,000 people)**
- Heart attack.
- chest pain
- shortness of breath
- discomfort in your upper body

❖ **Not known (frequency cannot be estimated from the available data**)
- Heart failure.
- shortness of breath
- extreme tiredness
- swelling in your legs, ankles, or feet

Module 8: Adverse Drug Reaction (ADR) Monitoring Form.

<table>
<tr><td>Report Type:- Initial</td><td>For AMC/NCC Use only</td></tr>
<tr><td>PATIENT INFORMATION</td><td>AMC Report No. :- 0020120</td></tr>
<tr><td>1. Patient Initials :-Jadhav .N.S.
2. Age at time of Event :-40
3. Sex :- Female
4. Weights :- 55 kgs</td><td>Worldwide Unique No :- 00210
12 . Relevant tests / Laboratory data With Dates:-TSH Test thyroid function tests Date :- 10/10/2022</td></tr>
<tr><td>Suspected Adverse Reaction
Date of reaction started:-08/10/2022</td><td>13 .Relevant medical/ medication history (e.g. allergies, pregnancy, smoking, alcohol use, hepatic/renal dysfunction etc.)
Hypertension ,</td></tr>
<tr><td>5. Date of recovery :-15/10/2022</td><td>14 .Seriousness of the reactions:- Hospitalization</td></tr>
<tr><td>6. Describe Reaction or Problem :- The Patient Was Taking Thyroxin Sodium Since 8/08/2022 , she Developed Weight Gain And Dry Skin Since 08/10/2022 . Examination Revealed Increased Sensitivity To Cold , Constipation, Hoarseness , Puff Face ,Hair loss . A Patient Was admitted On 10/10/2022 And Investigated . TSH Test Indicated Low Level Of thyroxine And High level of TSH In blood . Drug Were Discontinue. On Discontinuation Of Drug, Reaction Subsided In</td><td></td></tr>
</table>

International Journal of Pharmaceutical Research and Applications
Volume 8, Issue 6 Nov-Dec 2023, pp: 809-821www.ijprajournal.com ISSN: 2249-7781

One Week .	
C. Suspected Medication(S)	

Sr.No	Name (Brand / Generic	Manufacturer	Batch No.	Exp.Date	Dose Used	Route Used	frequency	Therapy Date		Indication	Causality Assessment
								Date Started	Date Stopped		
1.	Thyroxine Sodium	Abbot India Limited	AEG 2855	02/8/23	100mcg	Oral	BD	8/8/2022	8/10/2022	Hypothyroidism	Probable

9. Action Taken						10. Reaction Reappeared after reintroduction				
Sr.no	Drug Withdrawn	Dose Increased	Dose Reduced	Dose Not Changed	Not Applicable	Unknown	Yes	No	Effect Unknown	Dose (If reintroduced
1.	✓							✓		
2.										

11. Concomitant medical product including self-medication and herbal remedies with therapy dates (Exclude those used to treat reaction)

Sr.no	Name	Dose Used	Route Used	Frequency	Therapy Dates		Indication
					Date Started	Date Stopped	

Reporter Details

Module 9: Hospital Visit

On Date 15th November I Visited A Hospital The Name Of Hospital Is **Shirsath Hospital** Located At Ward No.1Court Cross Road, Shrirampur-Newasa Rd, Shrirampur, 413709. Where **DoctorShirsath Sir** Who Give Me Information Regarding Various Reported And Unreported ADR Of Thyroxin Sodium

TheThyroxin sodium isthe Drug that used as the Levothyroxine forthe treatment Of Hypothyroidism.. These Medications Work provide body a thyroid hormone.

The Doctor Said That Commonly Thyroxin Sodium Caused Various Adverse Reaction increased appetite, weight loss,heat sensitivity,excessive sweating,headache. Sensitivity Of The Skin To Sunlight. There Are Various Unreported ADR Of Thyroxin Sodium that patient ignored such as **m**ovements that you cannot control, mainly of the that produces imbalance in the body.

Module 10: Patient Interview

On same date Doctor Introduced me to A patient Name **Mrs. Jadhav.N.S.Age 40,Who** Suffering From Hypothyroidism, And She take Thyroxine sodium as a treatment for Hypothyroidism. Form Last 08/**08/2022**

After taking the medication She spotted that she developed a Weight Gain And Dry Skin and hair loss Since 08/10/2022. Examination Reviled Increased Sensitivity To Cold , Constipation, Hoarseness , Puff Face , Hair loss . Mrs jadhav told that after intake of Thyroxin Sodium after few time she started noticing Wheight Gain ,Hair loss &TSH Imbalance**.**

International Journal of Pharmaceutical Research and Applications
Volume 8, Issue 6 Nov-Dec 2023, pp: 809-821www.ijprajournal.com ISSN: 2249-7781

Module 11: Assessment of ADR

Sr.No	Question	Yes	No	Do Not Know	Score
1.	Are there previous conclusive reports on this reaction?	+1	0	0	0
2.	Did the adverse event appear after the suspected drug was administered?	+2	-1	0	+2
3.	Did the adverse reaction improve when the drug was discontinued or a specific antagonist was administered?	+1	0	0	0
4.	Did the adverse event reappear when the drug was re□administered?	+2	-1	0	0
5.	Are there alternative causes (other than the drug) that could on their own have caused the reaction?	-1	+2	0	0
6.	Did the reaction reappear when a placebo was given?	-1	+1	0	+1
7.	Was the drug detected in blood (or other fluids) in concentrations known to be toxic?	+1	0	0	0
8.	Was the reaction more severe when the dose was increased or less severe when the dose was decreased?	+1	0	0	+1
9.	Did the patient have a similar reaction to the same or similar drugs in any previous exposure?	+1	0	0	0
10.	Was the adverse event confirmed by any objective evidence?	+1	0	0	+1
				Total Score	+5

Report :- According To Naranjo Scale Algorithm ADR Causalty Assessment Was **Probable.**

CONCLUSION :-

For all medicines there is a trade-off between the benefits and the potential for harm. To minimize the harm, it is necessary that medicines of good quality, safety and efficacy are used rationally, and that the expectations and concerns of the patient are taken into account when therapeutic decisions are made. To achieve, this is to serve public health, and to foster a sense of trust in patients in the medicines they use that would extend to confidence in the health service in general.

The discipline of pharmacovigilance should be developed considerably day by day, and it remains a dynamic clinical and scientific discipline. It has been essential to meet the challenges of the increasing range and potency of medicines (including vaccines), which carry with them an inevitable and sometimes unpredictable potential for harm.The risk of harm, however, is less when medicines are used by an informed health profession and by patients who themselves understand and share responsibility for their drugs. When adverse effects and toxicity appear – particularly when previously unknown in association with the medicine – it is essential that they should be analyzed and communicated effectively to an audience that has the knowledge to interpret the information

Problems resulting from: irrational drug use, overdoses, polypharmacy and interactions, increasing use of traditional and herbal medicines with other medicines, illegal sale of medicines and drugs of abuse over the Internet, increasing self medication practices, substandard medicines, medications errors, lack of efficiency. This is the role of pharmacovigilance.

International Journal of Pharmaceutical Research and Applications
Volume 8, Issue 6 Nov-Dec 2023, pp: 809-821www.ijprajournal.com ISSN: 2249-7781

REFERENCE :-

[1]. "Essential of medical pharmacology" Seventh edition By K.D Tripathi, Published by- Jypee Brothers Medical publisher,
[2]. Page No :- 82-91.
[3]. Basic & Clinical Pharmacology By Bertram G. Katzung, FourteenthEdition,published by-Mc Graw Hill, Page No:- 346
[4]. Pharmacology And Pharmacotherapeutics , Twenty fifth edition,By R.S. Satoskar, Nirmala N. Rege , S.D. Bhandarkar ,Published by-Elsevier ,Page no:-839
[5]. Goodman & Gilman's The Pharmacological Basis Of Therapeutics 12th Edition By Laurene L. Brunton, Bruce A. Chabner, published by-Mc Graw Hill. Page No :- 798

Links :-

- https://en.wikipedia.org/wiki/Pharmacovigilance.
- https://www.aiims.edu/aiims/departments_17_5_16/pharmacology/pvpi/pvpi.htm#4.1%C2%A0%C2%A0%C2%A0%C2%A0%C2%A0_Goal.
- http://www.pharmabiz.com/PrintArticle.aspx?aid=63422&sid=18.
- https://database.ich.org/sites/default/files/E2A_Guideline.pdf.
- https://en.m.wikipedia.org/wiki/Naranjo_algorithm.
- https://www.ncbi.nlm.nih.gov/books/NBK548069/.
- https://go.drugbank.com/drugs/DB00451
- https://www.ncbi.nlm.nih.gov/books/NBK539808/
- https://pubmed.ncbi.nlm.nih.gov/20551006/
- https://www.pfizermedicalinformation.com/en-us/levoxyl/clinical-pharmacology
- https://medlineplus.gov/druginfo/meds/a682461.html
- https://www.goodrx.com/conditions/hypothyroidism/is-my-thyroid-medication-working-these-drugs-can-cause-interactions
- https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6822816/