DRUG INDUCED PARKINSONISM – A CAUSALITY, SEVERITY AND PREVENTABILITY ASSESSMENT STUDY IN A TERTIARY CARE HOSPITAL

Dissertation submitted to

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CERTIFICATE

This to certify that the dissertation entitled **"Drug Induced Parkinsonism – A Causality, Severity, and Preventability Assessment Study In A Tertiary Care Hospital"** by the candidate **Dr. P.Priya** for **M.D. Pharmacology (Branch VI)** is a bonafide record of the research done by her during her course period **(2014 -2017)** in the Department of Pharmacology, Kilpauk Medical College, Chennai – 600010.

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DECLARATION

I solemnly declare that this dissertation entitled **"Drug Induced Parkinsonism – A Causality, Severity, and Preventability Assessment Study In A Tertiary Care Hospital"** was written by me in the Department of Pharmacology, Kilpauk Medical College, Chennai, under the guidance and supervision of **Prof. Dr.C.Ramachandra Bhat, M.D.,** Professor and Head, Department of Pharmacology, Kilpauk Medical College, Chennai – 600 010.

This dissertation is submitted to **THE TAMILNADU Dr. M.G.R MEDICAL UNIVERSITY** Chennai, in partial fulfillment of the university regulations for the award of **DEGREE OF M.D PHARMACOLOGY (BRANCH - VI)** examinations to be held in **APRIL– 2017.**

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INSTITUTIONAL ETHICAL COMMITTEE
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Protocol ID. No.03/07/2015 Meeting held on 04/06/2015

CERTIFICATE OF APPROVAL

The Institutional Ethical Committee of Govt. Kilpauk Medical College, Chennai reviewed and discussed the application for approval "Drug induced parkinsonism a causality, severity & Preventability assessment study in a teritiary care hospital – For Dissertation Purpose" submitted by Dr.P.Priya, Post Graduate in MD (Pharmacology), Govt. Kilpauk Medical College, Chennai-10.

The Proposal is APPROVED.

The Institutional Ethical Committee expects to be informed about the progress of the study any Adverse Drug Reaction Occurring in the Course of the study any change in the protocol and patient information /informed consent and asks to be provided a copy of the final report.

GOVT. KILPAUK MEDICAL COLLEGE ★ Kilpauk, Chennai-10. ★
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CONTENTS

ABBREVIATIONS

WHO	-	World Health Organisation
ADRs	-	Adverse Drug Reactions
DIDM	-	Drug Induced Movement Disorder
DIP	-	Drug Induced Parkinsonism
PD	-	Parkinson's disease
TD	-	Tardive Dyskinesia
FGAs	-	First Generation Antipsychotics
SGAs	-	Second generation Antipsychotics
EPS	-	Extrapyramidal syndrome
PvPI	-	Pharmacovigilance Programme of India
CIOMS	-	Centre for International Organization of Medical Sciences
CDSCO	-	Central Drugs Standard Control Organization
MoHFW	-	Ministry of Health & Family Welfare
GOI	-	Government of India
SUSAR	-	Suspected unexpected serious adverse reaction
SSAR	-	Suspected serious adverse reaction
NCC	-	National Coordination Centre
AIIMS	-	All India Institute of Medical Sciences

IPC	-	Indian Pharmacopeia Commission
FDA	-	Food and drug administration
ICMR	-	Indian Council of Medical Research
AMC	-	ADR monitoring centres
ICSR	-	Individual Case Safety Report
UMC	-	Uppsala Monitoring centre
L- DOPA	-	L- 3, 4- dihydroxy phenylalanine
AADC	-	L- Aromatic Acid Decarboxylase enzyme
BBB	-	Blood Brain Barrier
VMAT-2	-	Vesicular Monoamine Tranporter
DAT	-	Dopamine Transporter
MAO	-	Monoamine Oxidase
COMT	-	Catecholamine – O- methyl transferase
DOPAC	-	3,4- Dihydroxyphenylacetic Acid
HVA	-	Homovanilic Acid
DA	-	Dopamine
5 HT	-	Serotonin
Type 2 DM	-	Type 2 Diabetes Mellitus
THP	-	Trihexyphenidyl
OPD	-	Out Patient Department

INTRODUCTION

A Drug is an active chemical molecule used for diagnosis, prevention, and treatment of a disease.[1] These Drugs when prescribed for medical illness also produce adverse effects which manifest differently according to various systems involved.

WHO definition : "Adverse drug reaction is defined as any noxious or unintended response to a drug, which occurs at doses normally used in man for prophylaxis, diagnosis or therapy of disease, or for modification of physiological function" .[2]

About 0.1% of medical and 0.01 % of surgical patients die due to adverse drug reactions. Although the magnitudes of patients affected by ADRs are few, they grossly affect the quality of life.

The morbidity and mortality associated with adverse effects of drug are often underestimated, as they present as diagnostic problems because they involve every organ and system of the body. They are commonly mistaken for signs of underlying disease, resulting in increase in the costs of patient care because of unnecessary investigations, delay in treatment, prolonged hospitalization, and added to it is the cost of treatment of ADRs as such.

Drug-induced movement disorders (DIDM) include tardive dyskinesia (TD), drug-induced Parkinsonism (DIP), akathisia, tardive dystonia, tremor,

and myoclonus. Among these, DIP is the most common drug induced movement disorder.[3]

In the elderly, after Parkinson's disease (PD), Drug-induced Parkinsonism (DIP) is the second-most-common cause of Parkinsonism. DIP may be misdiagnosed with PD because the clinical manifestations of DIP are very similar to those of Parkinson's disease (PD). Moreover in patients with DIP, neurological deficits are severe enough to affect their daily routine activities. Hence these patients are commonly prescribed with antiparkinsonian drugs which will not improve the condition, for longer periods of time unnecessarily, despite the fact that recovery being possible by simple measure of discontinuing the offending drugs. [4]

DIP may be caused by typical antipsychotics, gastrointestinal prokinetics, calcium channel blockers, atypical antipsychotics, and antiepileptic drugs. Among these typical antipsychotics is the most common offending drug to cause DIP. Even though atypical antipsychotics are less potential to cause DIP, they cannot be totally excluded.

Although, such adverse drug reactions are common, comprehensive information about their incidence, severity, and ultimate health effects are not available. Even though, there are published pharmaco-epidemiological studies from other countries on drug usage patterns in Parkinson's disease and DIP, till date there are only very few reported studies assessing the safety of the drugs commonly used in such clinical setting especially in India.

Hence this study was done to assess causality, severity, preventability of DIP in patients attending the Psychiatry and Neurology clinic and to highlight the need for awareness for this iatrogenic condition and to evaluate the current trends in DIP.

REVIEW OF LITERATURE

HISTORY

The concern about the fact that a drug might cause both beneficial effects and harmful effects started to develop in 19th century.

1848 -a young girl named Hannah Greener was given anaesthesia with chloroform for treatment of in-growing toe nail & had died during anaesthesia due to ventricular fibrillation. A commission was set up by "The Lancet journal" to report the events related to anaesthesia and the reports were published in 1893. This incident became the forerunner of spontaneous reporting system for adverse drug reactions. But unfortunately this system was neither retained nor extended to report various ADRs.[5]

In 20th century, due to the introduction of a wide range of new drugs, the frequency and severity of ADRs began to get exposed. But its implications and importance were not considered seriously by the existing authorities.

In 1934, amidopyrine which was a component of many patent drugs was found to cause agranulocytosis and was then registered as Schedule 4 drug of the pharmacy and poisons act 1933.[6]

In 1937, elixir sulfanilamide preparation containing diethyl glycol (DEG) caused mass death toll of about more than 100. This report began to create awareness about the potential risk of ADRs and as a result "Federal food and drug act" was passed in USA in 1938.[7]

In 1961, thalidomide disaster came to the light, known to have caused nearly 6000-250000 neonates born with a condition known as phocomelia which was later attributed due to thalidomide prescribed for the pregnant mother without proper clinical trials.[8] This paved the way for setting up "Committee on the safety of drugs" (CSD) by UK govt in 1964 and subsequently yellow card system for reporting ADRs was introduced.

In 1968 under the guidance of WHO, International drug safety monitoring centre was setup in Uppsala, Sweden also known as "The Uppsala drug monitoring centre".

In 1972, pharmacovigilance centres were started initially in 10 countries which work in collaboration with WHO International drug safety monitoring centre.

In 1980s, a programme on drug development and use was launched in collaboration with WHO, by CIOMS- The Council for International Organizations of Medical Sciences.

In 1990s, the International Conference on Harmonization (ICH) adopted the regulations put forth by CIOMS. Both created a notable effect on drug regulation and its proper use.

In India, drug safety monitoring system was proposed in the year 1986 with 12 regional centres. Since then reporting system began to act in collaboration with WHO "The Uppsala monitoring centre" (UMC).

Widening the horizon

In 2005, “National Pharmacovigilance Programme of India” was launched with the support of WHO and funding aid from World Bank. Additional support was gained with the implementation of Schedule Y. So it is now mandatory to report all adverse events including those suspected serious adverse reactions occurring during clinical trials.[9]

WHO states that the ADRs database in Uppsala currently contains over three million reports of suspected ADRs.

Patient reporting system

A novel concept in pharmacovigilance is the consumer adverse drug reporting system. This system exists in 44 countries. This reporting system contributes about 9% of total adverse reactions reports.

HISTORY OF ANTIPSYCHOTICS IN RELATION TO MOVEMENT DISORDERS [10]

In 1952 – the first antipsychotic drug, Chlorpromazine was introduced into clinical practice which revolutionized the treatment of millions of patients with psychosis.

Then the phenothiazine group and several other classes of FGAs were synthesized which were grouped into drugs with lower potency and those with high potency.

Side effects like sedation, anticholinergic effects, postural hypotension, with low potency drugs lead to the development of more potent and more specific D_2 receptor blockers such as Haloperidol in 1968.

Problems with drug induced movement disorders went unnoticed until the introduction of high potency drugs. Since these high potent drugs were producing more EPS, search for newer drugs with lower propensity to cause EPS was deeply sought for and as a result of this extensive quest, SGAs were introduced which showed lower propensity to cause EPS.

Before the introduction of SGAs, a common practice was to increase the dose of high potency drugs, with a belief that the effective treatment for positive symptoms could only be attained at the cost of extrapyramidal side effects. This strategy resulted in an increased incidence of EPS and low compliance as the patients felt that the treatment was not worth the side effects.

Because of this, change in treatment approach came into effect with use of low potency drugs with weaker D_2 antagonism. This alternative approach in treatment modality was supported with introduction of lower potency D_2 antagonist, Clozapine, in 1990.

Subsequently, a number of SGAs were synthesized and now the clinical use with these drugs has overridden the conventional drugs.

After the large scale use of neuroleptics, a broad list of “drug induced extrapyramidal reactions” was reported. Apart from neuroleptics, many other drugs were also reported to cause similar reactions, hence the concept of “drug induced movement disorders” (DIMDs) was evolved in 1970s as a distinct clinical entity.

BASIC DEFINITIONS

- **Adverse effect** is defined as "any undesirable or unintended consequence of drug administration". It is a broad term, which includes all kinds of noxious effect – trivial, serious or even fatal.[11]
- **Adverse drug event** is defined as "any untoward medical occurrence that may present during treatment with a medicine, but which does not necessarily have a causal relationship with the treatment".[11]
- **Adverse drug reaction** is defined as "any noxious or unintended response to a drug, which occurs at doses normally used in man for prophylaxis, diagnosis or therapy of disease, or for modification of physiological function".[11]
- **Serious adverse reaction:** is defined as ADR which results in death, is life threatening, requires in-patient hospitalization or prolongation of existing hospitalization, results in persistent or significant disability or incapacity, or is a congenital anomaly/ birth defect. [11]
- **Side effect** is defined as "any unintended effect of a pharmaceutical product occurring at doses normally used by a patient which is related to the pharmacological properties of the drug. [11]
- **Signal** is defined as reported information on a possible causal relation between an adverse event and a drug, the relation being previously unknown or incompletely documented. Usually more than one report is required to generate a signal, depending on the seriousness of the event and the quality of the information.[12]

- **Dechallenge:** [13]

  With type A reaction (dose dependent) : it means reducing the dose of a drug or stopping the drug altogether. With type B reaction (Bizarre): it means stopping the drug.

- **Rechallenge:** [13]

  It means restarting a drug after stopping it.

CLASSIFICATION OF ADR

ADR is classified into many types based on type of effect, causality, severity, preventability, dose, frequency, and time.

A) CLASSIFICATION BASED ON TYPE OF EFFECTS: (Pharmacological classification)[14]

Two principle types of ADR:

1. **Type A (Augmented):** these reactions are predictable and based on pharmacological properties of the drug. They are dose related and are more common. They are reversible and preventable. Ex: hypoglycaemia caused by insulin injection.
2. **Type B (Bizarre):** these reactions are due to the peculiarities of the patient and not due to drug effect. They are not dose related and are less common. They are fatal and more serious, mandating withdrawal of the drug. Ex: anaphylaxis caused by penicillin.

Four subordinate types

1. **Type C (Continuous/ chronic):** reactions occurring during long term use of drugs. Cushing's syndrome caused on prolonged use of prednisolone.
2. **Type D (Delayed effects):** adverse effects that occur lately from therapy for many years. Ex: secondary cancer due to use of alkylating agents for Hodgkin's disease.
3. **Type E (End of use):** adverse effects occurring after abrupt discontinuation of the drug. Ex: adrenocortical insufficiency after withdrawing corticosteroids.
4. **Type F (Failure of therapy):** failure of oral contraceptive therapy when given along with enzyme inducer

B) CLASSIFICATION ACCORDING TO THE SEVERITY[16]

1) Mild - Bothersome but requires no change in therapy.

2) Moderate-Requires change in therapy, additional treatment, hospitalization. Definite biochemical or structural changes occurs due to moderate involvement of vital organs.

3) Severe - Potentially life threatening, causing permanent damage. Definitely require hospitalization due to severe impairment of vital organs.

C) WHO CAUSALITY CLASSIFICATION[15]

CAUSALITY	ASSESSMENT
Certain	• Event or laboratory test abnormality, with plausible time relationship to drug intake • Cannot be explained by disease or other drugs • Response to withdrawal plausible(pharmacologically, pathologically) • Event definitive pharmacologically or phenomenological(i.e. an objective and specific medical disorder or a recognized pharmacological phenomenon) • Rechallenge satisfactory, if necessary
Probable/Likely	• Event or laboratory test abnormality, with reasonable time relationship to drug intake • Unlikely to be attributed to disease or other drugs • Response to withdrawal clinically reasonable • Rechallenge not required
Possible	• Event or laboratory test abnormality ,with reasonable time relationship to drug intake • Could not be explained by the disease or other drugs • Information on drug withdrawal may be lacking or unclear
Unlikely	• Event or Laboratory test abnormality with a time to drug intake that makes a relationship improbable(but not impossible) • Disease or other drugs provide plausible explanations
Conditional/ Unclassified	• Event or Laboratory abnormality • More data for proper assessment needed, or • Additional data under examination
Unassessable / Unclassifiable	• Report suggesting an adverse reaction • Cannot be judged because information is insufficient or contradictory • Data cannot be supplemented or verified

D) CLASSIFICATION ACCORDING TO SERIOUSNESS [17]

1) Suspected Unexpected Serious Adverse Reaction (SUSAR)

2) Suspected Serious Adverse Reaction (SSAR)

Both results in death, life threatening situations and require intervention to prevent permanent damage. Both may result in disability and also causes congenital anomalies.

E) CLASSIFICATION BASED ON DOSE RELATIONSHIP [18]

1) Dose related: a) Pharmaceutical variation b) Pharmacokinetic variation – Pharmacogenetic variation, hepatic disease, renal disease, cardiac disease, thyroid disease, drug interactions. c) Pharmacodynamic variation - Hepatic disease, altered fluid and electrolyte balance, drug interactions.

2) Non-dose-related: a) Immunological reactions b) Pseudoallergic reactions c) Pharmacogenetic variation.

3) Long term effects: a) Adaptive changes b) Rebound phenomenon c) Other long term effects.

4) Delayed effects: a) Carcinogenesis b) Effects concerned with reproduction- 1) impaired fertility 2) Teratogenesis- Adverse effects on the foetus during early pregnancy, late pregnancy 3) Adverse effects due to drugs in breast milk

F) FREQUENCY CLASSIFICATION[19]

Report from CIOMS (Centre for international organization of medical sciences) working group III, Geneva 1995

1) Very common (Optional) : >10%

2) Common (Frequent) : >1% and ≤ 10%

3) Uncommon (Infrequent) : >0.1% and ≤ 1%

4) Rare : 0.01% and ≤ 0.1%

5) Very rare (Optional) : <0.01%

G) REACTION TIME CLASSIFICATION[20]

Reaction time is defined as the time between the last drug exposure and the appearance of the first symptoms.

1) Acute : 0-60 Minutes (4.3 % of reactions)
2) Sub-acute : 1-24 Hours (86 % of reactions)
3) Chronic : day to several weeks (3.5% of reactions)

PHARMACOVIGILANCE

Pharmacovigilance is defined as "the science and activities relating to the detection, assessment, understanding and prevention of adverse dugs reactions or any other drug related problems" [21].

Aims of Pharmacovigilance: [21]

1. To enhance patient care and safety in relation to the use of medicines;
2. To support the public health programmes by providing more reliable and balanced information for the effective assessment of the benefit – risk profile of medicines,
3. To improve public health and safety in relation to the use of medicines,
4. To contribute the assessment of effectiveness, benefit, risk and harm of medicines, encouraging their effective (including cost effective), rational and safe use,

5. To promote clinical training, education and understanding in pharmacovigilance ,
6. To promote effective communication about pharmacovigilance to the public.

Classical examples of serious and unexpected adverse reactions [21]

Medicine	**Adverse reaction**
Aminophenazone (amidopyrine)	Agranulocytosis
Chloramphenicol	Aplastic anaemia
Clioquinol	Myelooptic neuropathy
Erythromycin estolate	Cholestatic hepatitis
Methyldopa	Haemolytic anaemia
Oral contraceptives	Thromboembolism
Reserpine	Depression
Statins	Rhabdomyolysis
Thalidomide	Congenital malformations

WHO PROGRAMME FOR INTERNATIONAL DRUG MONITORING[21]

In 1968, WHO's Programme for International Drug Monitoring was started with the concept of pooling existing data on ADRs. A pilot project with established national reporting systems for ADRs was started initially in10 countries. Since then the network has expanded to include many more countries, co-ordinated by WHO, under “The Upssala Monitoring Centre”, Sweden. This centre maintains the global ADR database known as “Vigibase”. Currently the database contains more than 3 million reports in it.

The Upssala Monitoring Centre analyses the reports in the database:

- To identify the early warning signals of serious adverse reactions to medicines;
- To undertake research to aid the development of more effective and safer medicine;
- To evaluate the hazard.

ROLE OF PHARMACOVIGILANCE [21]

- To serve public health, and to provide a sense of trust among patients in the medicines they use that would create a confidence in the health service;
- To ensure that the risks in drug use are anticipated and managed effectively;
- To provide the regulators with all the necessary information to amend the recommendations on the proper use of the medicines;
- To improve the communication between the public and the health professionals;
- To educate the health professionals to understand the benefit and risk of medicines that they prescribe.

MONITORING THE SAFETY OF MEDICINES: KEY PARTNERS [21]

- World Health Organization
- Government
- Hospitals and academia

- Medical and pharmaceutical associations
- Poisons and medicines centres information
- Health professionals
- Patients
- Consumers
- Media
- Industry

SPONTANEOUS REPORTING SYSTEM

A spontaneous report is an unsolicited communication given by the healthcare professionals or the consumers to a regulatory authority, company, or other organization like WHO-regional centre / poison control centre. This report describes about one or more adverse drug reactions occurring in a patient who was prescribed one or more medicinal product that does not derive from a study or any organised data collection scheme.[22] Spontaneous report system has paved way for identification of signal.

SIGNAL

Signal is the possible relationship between a drug and an adverse event, the relationship being unknown or incompletely documented previously.[23] More than one report is needed for signal generation.

IMPORTANCE OF REPORTING

When an adverse effect or toxicity appears especially when it is unknown previously, it is essential that they should be reported, analysed and

their significance should be effectively communicated to an audience who has the knowledge to interpret the information and create an awareness globally.

PHARMACOVIGILANCE PROGRAMME OF INDIA (PvPI) [24]

CDSCO (Central Drugs Standard Control Organization), under the aid of Ministry Of Health & Family Welfare (MoHFW), Government of India (GOI) in collaboration with All India Institute of Medical Sciences, New Delhi as the National Coordination Centre (NCC), has initiated a nationwide pharmacovigilance programme for protecting the health of the patients by ensuring drug safety in July 2010. To ensure the effective implementation of the programme, the NCC was shifted from AIIMS to Indian Pharmacopeia Commission (IPC), Ghaziabad on 15th April 2011. IPC is an autonomous institution of MoHFW, GOI. This centre will operate under the guidance of a steering committee. In 2010 PvPI was started with 22 ADR monitoring centres (AMCs). Then new AMCs were added by the NCC-PvPI to strengthen the reporting of ADRs.

ADR reporting at PvPI: [24]

PvPI has spontaneous reporting system to collect data on drug safety. A spontaneous report is an unsolicited communication by health care professionals, or consumers, or pharmaceutical companies to the regulatory authority. To ensure this purpose the NCC has designed a **"Suspected Adverse Reaction Reporting Form".**

ICSR (Individual Case Safety Report) - is defined as "a report that contains information describing a suspected adverse reaction related to the administration of one or more medicinal products to an individual patient".

To encourage the direct participation of patients in the PvPI, IPC has launched the novel **"Medicines Side Effect Reporting Form for Consumers".** This form will be reported by the patient to the AMCs. This form is available in Hindi, Tamil, Gujarati, Oriya, Kannada, Malayalam, & Bengali. This empowers the patient to report the ADRs irrespective of the language barrier. Soon this form will be translated to other regional languages as well.

DOPAMINE [25]

HISTORY

- In 1910 - Dopamine was first synthesized
- In the same year, Henry Dale characterized the biological properties of dopamine and described dopamine as a weak, adrenaline like substance.
- In 1930 – dopamine was recognised as a transitional substance in the synthesis of epinephrine and norepinephrine.
- In 1950 – dopamine stores were found in tissues and was found to have signalling function of its own.
- 1n 1960 – Carlsson and Montagu- has discovered dopamine stores in the brain.

- Horneykiewicz – discovered the deficit of dopamine in Parkinsonian brain.
- These discoveries had fuled the interest in the role dopamine in neurological disorders in the susequent years.

CHEMISTRY:

Dopamine consists of a catechol moiety linked to an ethyl amine, and hence classified as catecholamine. Dopamine is a polar molecule, that doesnot cross blood brain barrier (BBB).

SYNTHESIS, STORAGE AND RELEASE:

The aminoacids like tyrosine, and phenylalanine serve as the precusors for dopamine synthesis. L-Phenylalanine is converted to L-tyrosine by the enzymatic action of phenylalanine hydroxylase. Tyrosine can cross readily into brain through uptake which is then converted to L-DOPA by tyrosine hydroxylase, which is the rate limiting step in dopamine synthesis. L-DOPA is rapidly converted ultimately into dopamine by L- aromatic acid decarboxylase (AADC) enzyme. AADC activity is very high in both CNS and periphery. L-DOPA readily crosses the BBB. L-DOPA is thus taken up into the storage vesicles by vesicular monoamine tranporter, VMAT-2. Then it is released into the synaptic cleft by exocytosis.

METABOLISM

The released dopamine is then subjected to both transporter clearance by DAT (dopamine transporter) and metabolism by MAO (monoamine oxidase) and COMT (Catecholamine – O- methyl transferase). Reuptake of dopamine by DAT is the primary mechanism of termination of dopamine action. Metabolism of dopamine is primarily done by MAO, localized both presynaptically and postsynaptically. MAO metabolizes dopamine into DOPAC (3,4- dihydroxyphenylacetic acid) . DOPAC is further metabolized by COMT into HVA (homovanilic acid). HVA is principal metabolite of dopamine in humans. In the periphery, COMT also metabolizes dopamine into 3-O-methyldopa.

DOPAMINE RECEPTORS [25]

Dopamine receptors are Metabotropic receptors or G- protein coupled receptors

There are 5 DA receptors: **D_1 to D_5**

Divided into 2 families

- **D_1 - like family**
  - Includes D_1 & D_5
  - Gs - Activates adenylate cyclase → ↑ cAMP
- **D_2 - like family**
  - Includes D_2 , D_3 , D_4
  - Gi - inhibits adenylate cyclase → ↓ cAMP
  - ↓K^+ currents
  - ↓ voltage gated Calcium currents

RECEPTOR DISTRIBUTION

D_1	D_2
Substatia nigra pars reticulata	Striatum
Frontal cortex	Substatia nigra pars compacta
Nucleus acumbens	Pituitary
Hypothalamus	Prefrontal cortex

DOPAMINE PATHWAYS [25]

- **Dopamine in brain projects via four main pathways -**

1. Mesolimbic pathway
2. Mesocortical pathway
3. Nigrostriatal pathway
4. Tuberoinfundibular pathway

SIGNIFICANCE OF EACH DOPAMINE PATHWAYS

MESOLIMBIC PATHWAY

Anatomy: Projects from ventral tegmental area to nucleus accumbens.

Physiology: It governs - motivation, reward, emotions & negative symptoms of schizophrenia.

Implication: in psychoses, schizophrenia, & in ADHD

MESOCORTICAL PATHWAY

Anatomy: projects from ventral tegmental area to prefrontal cortex.

Physiology: cognition & executive functions (DLPFC), emotions & affect (VMPFC)

Implication: Schizophrenia, ADHD

NIGROSTRIATAL PATHWAY

Anatomy: projects from substantia nigra (pars compacta) to striatum (caudate & putamen)

Physiology: co-ordination of movements

Implication: Parkinson's disease, DIP

TUBEROINFUNDIBULAR PATHWAY

Anatomy: hypothalamus to infundibular region

Physiology: dopamine inhibits prolactin release

Implication: D_2 antagonism causes hyperprolactinemia

ANTIPSYCHOTIC DRUGS: NEUROLEPTICS [25]

CLASSIFICATION:

I. Classical / Typical antipsychotics

1. Phenothiazines :

Chlorpromazine

Trifluprомazine

Thioridazine

Trifluoperazine

Fluphenazine

2. Butyrophenones

Haloperidol

Trifluperidol

Penfluridol

Thioxanthenes

Flupenthixol

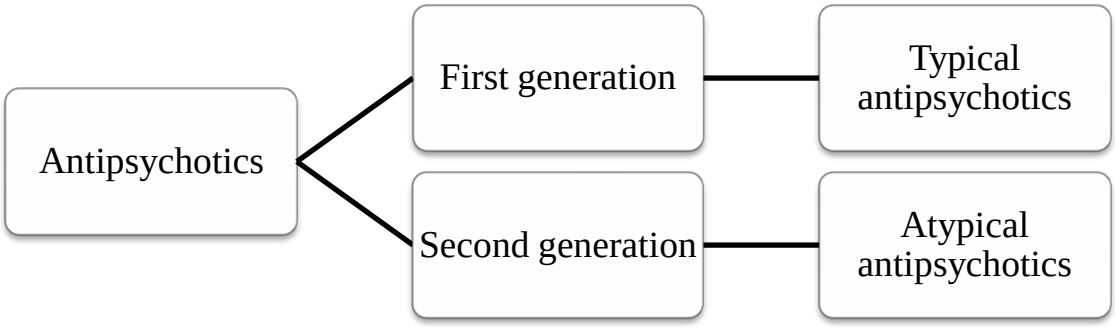
3. Other heterocyclics

Pimozide , Loxazipine

II. Novel /Atypical antipsychotics

Clozapine	Aripiprazole
Risperidone	Ziprasidone
Olazapine	Amisulpride
Quetiapine	Zotepine

Also classified as:



MECHANISM OF ACTION OF ANTIPSYCHOTICS [25]

TYPICAL ANTIPSYCHOTICS

All the typical antipsychotics have potent **D_2** receptor blocking effect. Reduction of dopamine transmission is their major mechanism of action. Their potency show good correlation with their ability to bind to D_2 receptor and to block them. Blockade of D_2 receptor in "limbic system & mesocortical" areas is responsible for the antipsychotic effect. In addition these drugs have **α_1** adrenergic blocking action, **M_1** muscarinic blocking action and **H_1** histaminergic blocking action.

The delayed onset of effects of these drugs is due to initial increase in release of dopamine from dopamine neurons. But on repeated drug administration, they enter a state of physiological depolarization inactivation, with gradual decrease in production and release of dopamine with continued receptor blockade.

ATYPICAL ANTIPSYCHOTICS

Atypical antipsychotics have more potent 5-HT_2 blocking action, and weak D_2 receptor blocking action in addition to α_1 adrenergic blocking action. Some of them are relatively selective for D_4 receptors. Thus antipsychotic action depends on specific profile of action of these drugs acting on various neurotransmitter receptors with varying binding activity.

ADVERSE DRUG EFFECTS OF ANTIPSYCHOTICS [25]

- **Classified into 2 broad categories**

- **Adverse effects predicted by monoamine receptor affinities**
- **Adverse effect not predicted by monoamine receptor affinities**

I. ADVERSE EFFECTS PREDICTED BY MONOAMINE RECEPTOR AFFINITIES

A) D_2 RECEPTOR BLOCKADE: leads to extrapyramidal side effects (EPS). Typical antipsychotics are more prone for EPS since they are potent D_2 blockers, while atypical antipsychotics cause less EPS as they are weak blockers. EPS consists of 6 categories. They are

1. Drug induced Parkinsonism
2. Acute muscular dystonia
3. Akathisia
4. Malignant neuroleptic syndrome
5. Perioral tremors
6. Tardive dyskinesia

PROFILE OF EXTRAPYRAMIDAL SYNDROMES

Syndromes	Features	Time of onset & risk info	Proposed mechanism	Treatment
Acute dystonia	Spasm of muscles, mostly linguo-facial muscles	1-5 days Young antipsychotic naïve patients are at risk	Acute dopamine antagonism	Resolves spontaneously, Central anticholinergics, promethazine or hydroxyzine
Parkinsonism	Bradykinesia, variable tremor, rigidity, shuffling gait, mask facies	5-30 days Elderly at greatest risk	Dopamine antagonism	Dose reduction Central anticholinergics, Amantadine, change of antipsychotics to atypical drugs
Akathisia	Restlessness, compelling desire to move about without anxiety	5-60 days	Unknown	Change drug or reduce dose Clonazepam, Propranolol, central anticholinergics
Neuroleptic malignant syndrome	Marked rigidity, fever, tremor, fluctuating BP, myoglobinemia, can be fatal	Weeks-months	Dopamine antagonism	Stop neuroleptics Supportive care, i.v. dantrolene, bromocriptine
Perioral tremor (rabbit syndrome)	Perioral tremors – late variant of parkinsonism	Months or years of treatment Elderly at 5-fold risk	Postsynaptic dopamine receptor supersensitivity, & neuronal degeneration	Treatment unsatisfactory, prevention crucial, may subside months or years after discontinuation of the drug

B) H_1 receptors:

Antagonism of H_1 receptors centrally causes two important side effects, sedation and weight gain via appetite stimulation. Low potency typical antipsychotic drugs like thioridazine and chlorpromazine, atypical antipsychotic drugs like clozapine and quietiapine possess high H_1 receptor affinity and hence cause more sedation.

C) M_1 receptors:

Muscarinic receptor antagonism is responsible for the peripheral and central anticholinergic effects. Most of the atypical antipsychotics have no muscarinic affinity, so no anti-muscarinic side effects are produced. But the drugs like Clozapine and low potency phenothiazines have marked and significant anti-musarinic adverse effects. The drugs with significant anticholinergic affinity should be avoided in elderly, particularly in those with dementia or delirium.

D) α_1 receptors:

α_1 adrenergic antagonism results in risk of orthostatic hypotension. These drugs should be avoided in elderly with poor vasomotor tone. Low potency drugs have more affinity towards α_1 adrenergic receptors when compared to high potency drugs and are greater risk of causing orthostatic hypotension.

II. ADVERSE EFFECT NOT PREDICTED BY MONOAMINE RECEPTOR AFFINITIES

A) ADVERSE METABOLIC EFFECTS:

These have become the greatest concern during long term antipsychotic drug treatment. There is high prevalene of Type 2 DM and prediabetic conditions, and 2-fold increase in cardiovascular mortality among those on antipsychotic drug treatment for longer duration. Also these patients suffer from weight gain, dyslipidemia, elevated TGL, and impaired glycemic control. Atypical drugs like Clozapine, Olanzapine and low potency phenothiazines have significant metabolic adverse effects.

B) ADVERSE CARDIAC EFFECTS:

Two most significant cardiovascular side effects are ventricular arrhythmia & sudden cardiac death. Most of the older antipsychotic drugs have the tendency to inhibit cardiac K^+ channels. All these antipsychotic drugs carry the label warning regarding QTc prolongation.

C) OTHER ADVERSE EFFECTS:

- Blue pigmentation of exposed skin, lenticular and corneal opacities, retinal degeneration, are more with thioridazine.
- Cholestatic jaundice – is more common with phenothiazines (low potency).
- Agranulocytosis – is rare and more common with clozapine.

- Myocarditis – is seen in few patients taking clozapine.
- Skin rashes, contact dermatitis, utricaria, and photosensitivity is more common with chlorpromazine.
- Lowering of seizure threshold in epileptic patients using antipsychotic drugs.

DRUG INDUCED MOVEMENT DISORDERS (DIMDs) [26]

Various Classifications

I. Classified based on their

A) Temporal profile

- Acute : those occurring within hours or days after exposure
- Subacute: developing slowly after days to weeks of exposure
- Chronic : developing after long term therapy with the offending drug

B) Phenomenology

- Dystonia, tremor, parkinsonism, dyskinessia, akathisia, myoclonus, chorea, tic

C) Drugs involved

- Neuroleptics – typical & atypical
- Other D_2 blockers
- Antidepressants
- Anti-epileptics
- Recreational drugs
- Toxins

II. Classification of Medication induced movement disorders[27]

A) Categorized into

1. Hypokinetic disorders – with paucity of movements

   (e.g. akinesia, bradykinesia)

2. Hyperkinetic disorders – with excessive movements

   (e.g. dyskinesia, akathisia)

B) Divided into those associated with use of

1. Antipsychotics (Neuroleptics)
2. Other psychotropic agents
3. Non- psychotropic agents

III. DSM-IV-TR: fourth edition of the "DIAGNOSTIC AND STATISTICAL MANUAL OF MENTAL DISORDERS"[28]

Categorises medication induced movement disorder into **7** categories

S.No	Category	Features
1	**Neuroleptic induced parkinsonism**	Triad of tremor, rigidity, and akinesia. Develops within a few weeks of starting or increasing the dose of the neuroleptics.
2	**Neuroleptic malignant syndrome**	Elevated temperature, severe muscular rigidity and other features developing after the use of neuroleptics.
3	**Neuroleptic induced dystonia**	Spasm or abnormal positioning of the muscles of head & neck, limbs or trunk. Develops within few days of starting or increasing the dose of the neuroleptics.

4	**Neuroleptic induced akathisia**	Subjective compliant of restlessness associated with observed movements. Develops within a few weeks of starting or increasing the dose of the neuroleptics.
5	**Neuroleptic induced tardive dyskinesia**	Involuntary choreiform, rhythmic, or athetoid movements of the jaw, tongue,or limbs developing after the use of neuroleptics.
6	**Medication induced postural tremor**	Fine tremor which occurs during an attempt to maintain a posture developing after the use of neuroleptics.
7	**Medication induced movement disorder not otherwise specified**	This category consists of medication induced movement disorders not classified by any of the above specific disorders

DRUGS ASSOCIATED WITH MOVEMENT DISORDERS AND THEIR IMPACT ON RECEPTORS[29]

Type	Name	D_2 blockade	5-HT_2 blockade	mACh blockade
ANTIPSYCHOTICS				
Phenothiazine	Chlorpromazine	L	H	H
Phenothiazine	Thioridazine	L	M	H
Phenothiazine	Trifluoperazine	M	M	M
	Fluphenazine	H	L	L
	Perphenazine	H	M	L
Thioxanthene	Thiothixene	H	M	L
Dibenzoxazepines	Loxapine	M	H	L
Butyrophenones	Haloperidol	H	L	L
	Droperidol	H	M	-
Diphenylbutyl piperidies	Pimozide	H	M	L
Dihydroindolones	Molindone	M	L	L

Dibenzodiazepine	Clozapine	L	H	H
Benzisoxazoles	Risperidone	H	H	L
	Paliperidone	H	H	L
Thienobenzodiazepines	Olanzapine	L	H	H
Dibenzodiazepine	Quetiapine	L/M	L/M	L
Benisothiazolyls	Ziprasidone	M	H	L
Quinolones	Aripiprazole	H (PA)	H	L
NON-ANTIPSYCHOTIC PSYCHOTROPICS				
Ions	Lithium	-	-	-
Anticonvulsants		L	L	L
Antidepressants		L (except Amoxapine)	Varies	Varies
NONPSYCHOTROPICS				
	Prochlorperazine	H	M	L
	Metoclopramide	H	H	-

H- High; **L**-Low; **M**- Medium

SPECTRUM OF DRUGS CAUSING ACUTE EPS [29]

Maximum			**Minimum**
……			
High potency FGAs	Risperidone Paliperidone	Olanzapine Ziprasidone Aripiprazole	Clozapine Quetiapine
…… (Dose related) ……			

RECEPTOR OCCUPANCY AND CLINICAL RESPONSE OF ANTIPSYCHOTICS[25]

- **D_2 RECEPTOR OCCUPANCY / D_2 ANTAGONISM:**
  - Receptor occupancy > 60% by the drug - provides antipsychotic effects
  - Receptor occupancy > 80% by the drug – causes extrapyramidal symptoms (EPS)
- **$5HT_2$ ANTAGONISM / INVERSE AGONISM:**
  - Atypical antipsychotics have more potent $5HT_2$ antagonism/inverse agonism with weak D_2 receptor blockade leading to reduced EPS

PROKINETIC DRUGS [1]

- These drugs promote gastric transit and increase the gastric emptying by enhancing propulsive motility.
- Drugs in this category are metoclopramide and domperidone. These drugs act by D_2 antagonism.

Features	Metoclopramide	Domperidone
Mechanism of Action	D_2 antagonism $5HT_2$ and $5HT_3$ antagonism	D_2 antagonism
Adverse effects	Sedation, muscular dystonia, dizziness, loose stools **On long term use :** Parkinsonism, galactorrhea, and gynaecomastia	Galactorrhea, , loose stools, headache, and rashes, EPS rare

DRUG INDUCED PARKINSONISM (DIP) [26]

DIP is defined as Parkinsonism secondary to medications. DIP is the second most common form of Parkinsonism after Parkinson's disease in the elderly.

EPIDEMIOLOGY [30]

DIP is often misdiagnosed as Parkinson's disease, hence exact incidence and prevalence are not clearly known. Chlorpromazine (CPZ) was the first antipsychotic drug to be studied for extapyramidal side effects, which stated that about 40% of patients on CPZ developed drug induced Parkinsonism. A population based survey and a community based survey found that the prevalence rate of DIP was 1.7% and 2.7% respectively, whereas the prevalence rate of Parkinson's disease was 4.5% and 3.3% respectively. But 6.8% of patients who have been diagnosed with Parkinson's disease was later rediagnosed as having DIP, which clearly emphasises the difficulties in classifying the patients as DIP or Parkinson's leading to unclear prevalence.

Age is the most common risk factor for DIP and found to be more common in elderly (> 60yrs). Gender is another risk factor in which females are more susceptible which suggests that oestrogen plays a role in suppression of the expression of the dopamine receptors. Genetic factors may also play a role in the manifestation of DIP, because all the patients who are taking dopamine receptor blocking drugs do not develop DIP. Genetic screening may help to find the vulnerable patients but it is not practically possible in the developing countries.

ETIOPATHOLOGY [25]

DIP results from deficiency of dopamine in nigrostiatal dopamine pathway. This can be caused by

- **Main causative agents like**
  - Dopamine depleters, (e.g., reserpine),
  - Dopamine blocking agents (e.g. Antipsychotics),
  - Calcium channel blockers (e.g. Cinnarazine),
  - Antiemetics (e.g. Metoclopramide).
- **Other drugs causing DIP:** are antiepileptics, antidepressants & anticancer drugs
- **Toxins causing DIP:** are MPTP, OPC, methanol, manganese,cyanide, & CO.

DRUGS FREQUENTLY CAUSING DRUG INDUCED PARKINSONISM- (Higher risk) [30]

Typical Antipsychotics	**Phenathiazine:** Chlorpromazine, Prochlorperazine, perphenazine, fluphenazine, promethazine **Butyrophenones:** Haloperidol **Diphenylbutylpiperidine:** Pimozide **Benzamide substitutes:** Sulpiride
Atypical Antipsychotics	Risperidone, Ziprasidone, Olanzapine, Aripiprazole
Dopamine depleters	Reserpine, Tertrabenazine
Antiemetics	Metoclopramide, Levosulpride, Clebopride
Calcium channel blockers	Flunarazine, Cinnarazine

DRUGS INFREQUENTLY CAUSING DRUG INDUCED PARKINSONISM - (Intermediate risk) [30]

Atypical antipsychotics	Clozapine, Quetiapine
Mood stabilizer	Lithium
Antidepressants	SSRI: Citalopram, Fluoxetine, Paroxetine, Sertraline
Antiepileptic dugs	Valproic acid, Phenytoin
Antiemetics	Domperidone, Itopride

DRUGS RARELY CAUSING DRUG INDUCED PARKINSONISM – (Lower risk) [30]

Antihypertensives	Diltiazem, Captopril
Antiarrythmics	Amiodarone, procaine
Antidepressants	Fluoxetine, TCAs, MAO inhibitors- Phenelzine
Immunosuppressants	Cyclosporine, tacrolimus
Antibiotics	Co-trimoxazole
Antifungals	Amphotericin – B
Antivirals	Vidarabine, Acyclovir
Chemotherapeutics	Cytosine arabinoside, Ifosfamide, Vincristine
Hormones	L-Thyroxine, Medroxyprogesterone
Statins and Others	Lovastatin, Donepezil, Bethanecol, Pyridostigmine

CLASSIC TRIAD OF SYMPTOMS: [30]

- All three symptoms may be present, but only one is required for the diagnosis.

OTHER SYMPTOMS

- Are Speech difficulties (poverty of speech), gait disturbances (shuffling gait), expression less face.

DIP VERSUS PARKINSON'S DISEASE [30]

DIP	Parkinson's disease
Symptoms – symmetrical	Symptoms – asymmetrical
Onset – acute or subacute	Chronic
Reversible once the offending drug is stopped	Chronic & progressive
Postural tremor	Resting tremor
Subacute onset after starting the drug	Slow, progressive course
Not responsive to antiparkinson drug treatment	Responsive to antiparkinson drug treatment
Caused by drugs	No known cause
No brain degeneration	Brain degeneration +
More common in females	More common in males
Associated features: Akathisia and Orobuccal dyskinesia are present	Absent
Motor fluctuations absent	Motor fluctuations present

RISK FACTOR FOR DEVELOPMENT OF DIP: [31]

- High dose of neuroleptics
- High potency neuroleptics
- Piperazine side chain chain neuroleptics
- Females (F:M ratio is 2:1)
- Elderly
- Preclinical Parkinsonism
- Co-existence of tardive dyskinesia
- AIDS

CLUES TO DIAGNOSE DIP CLINICALLY: [31]

- Presence of symptoms of DIP
- Symmetrical
- Exposure to a drug +
- Onset of DIP symptoms during the use of offending drug
- No history of DIP before starting the offending drug
- Progression of symptoms in relation to mediation intake
- Early presence of postural tremor
- Concurrent presence of oral-buccal dyskinesia

RADIOLOGICAL DIAGNOSIS [30]

Dopamine transporter (DAT) imaging: is useful for diagnosing presynaptic Parkinsonism. DAT uptake in nigrostriatum is markedly decreased even in the early stages of PD, since the motor symptoms in PD appear only

when 60-80% of dopaminergic neurons degenerate. This feature helps to differentiate PD from DIP

Single – photon emission tomography (SPECT) and positron- emission tomography (PET) scans are used for DAT ligands. The drugs which cause DIP have negligible affinity to DAT. In DIP, DAT scans shows symmetrical uptake of radiotracer in the bilateral striatum in those patients affected by pure DIP, but in those with PD, DAT shows decreased and asymmetrical uptake in the striatum.

PREVENTION OF DIP [30]

- Identify high risk population and avoid prescribing offending drugs in them
- Avoid unnecessary medications
- Wise and judicious use of favorable medications
- Using lowest dose of drugs
- Avoid unnecessary prolonged therapy
- Elicit proper drug history and its previous adverse effects

TREATMENT OF DIP [25]

- Cessation of offending drugs.
- Switch to another drug which has lower propensity to cause DIP (typical antipsychotic drug to atypical antipsychotic drug).
- Dose reduction in those who respond only to the given drug.

- Treatment with centrally acting anticholinergics which includes trihexyphenidyl (THP), benztropine. Usually THP is given at the dose of 2 mg twice daily.
- Amantadine is also used o treat DIP which is equally effective as anticholinergics.

OUTCOMES OF DIP [30]

Usually DIP resolves within weeks to months after the cessation of the offending drug. Sometimes DIP may progress or persists in 10- 50% of patients.

- Outcome falls into 4 types.
    1. Complete and long lasting recovery with no subsequent development of Parkinsonism
    2. Persistence but progressing to Parkinsonism
    3. Persistence and progression to Parkinsonism
    4. Full recovery and remission, but reappearance in later stages after discontinuing the offending drug
- Only those patients falling under type 1 & 2 are classified as having pure DIP, whereas those patients classified under 3 & 4 may be in the preclinical stages of PD.

AIM AND OBJECTIVES OF THE STUDY

PRIMARY OBJECTIVE

- To analyze the different group of drugs causing drug induced Parkinsonism (DIP).

SECONDARY OBJECTIVES

- To describe the Causality analysis of drug induced Parkinsoism using **WHO causality assessment scale and Naranjo algorithm.**[32]
- To describe the severity analysis of drug induced Parkinsoism by using **Hartwig and Siegel scale.**[33]
- To describe the preventability assessment by using **Modified Schumok and Thorton Scale**. [34]
- To describe the profile of manifestations of DIP.
- To describe the socio-demographic profile in DIP.
- To analyze the predisposing factors for DIP.

METHODOLOGY

MATERIALS AND METHODS

- **Study design:** Descriptive study - A Cross Sectional Study
- **Study period:** June 2015 to June 2016
- **Study duration:** One year
- **Study centre:** Out- patient department of Psychiatry and Neurology
- **Study population:** Patients diagnosed with drug induced Parkinsonism attending the out- patient department of Psychiatry and Neurology
- **Sample size:** All the patients diagnosed with drug induced Parkinsonism attending the out- patient department of Psychiatry and Neurology during the period of one year.

INCLUSION CRITERIA

- Patients of all ages, of either gender presenting to the out- patient department of Psychiatry and Neurology with drug induced Parkinsonism.
- Patients referred from other specialities to the department of Psychiatry and Neurology OPD for the treatment of DIP.

EXCLUSION CRITERIA

- Patients with Parkinson's disease
- Patients not willing to participate in the study

ETHICS CONSIDERATION

- The study was approved by the institutional ethics committee.
- Confidentiality and identity of the patient's information were maintained during and after the study
- Care and treatment of the patient was not interfered during the study period.

STUDY PROCEDURE

All the patients diagnosed with DIP, attending the department of Psychiatry and Neurology OPD was registered after obtaining proper informed consent. Since the study was undergone in Psychiatry, for those patients who were unable to give consent, the consent was obtained from their guardian accompanying them. Those with Parkinson's disease were excluded from the study.

All the details of the patient like basic demographic data, presenting illness, past medical history, any associated co-morbidites, family history and usage of concomitant medications were collected and recorded in the proforma. The diagnosis of DIP was confirmed by the Psychiatrist and Neurologist. Detailed clinical history and physical examination was done by the Psychiatrist and Neurologist before arriving to the diagnosis of DIP. After their diagnosis, details of the manifestations of DIP and the drugs suspected to cause DIP were collected and recorded in the proforma. Complete prescription details before and after the manifestation of DIP was collected and recorded.

All the information was recorded in the "Suspected Adverse Drug Reporting Form" given by Central Drugs Standard Control Organisation (CDSCO), New Delhi. While uploading the form, only the patient initials not their name was recorded to maintain the confidentiality and privacy of the patient. The following were the data's recorded in the form,

- Demographic data- age, sex, weight
- Details of manifestation of DIP: like description of the reaction, onset and recovery of the reaction
- Details of the suspected drug causing ADR
- Details of the concomitant medications
- Relevant and other past medical history
- Relevant laboratory investigations
- Seriousness of the reaction
- Outcome of the reaction

ASSESSMENT: Totally 50 patients with DIP were enrolled in the study over the study period of one year.

- All these data were analyzed and causality assessment was done using **WHO causality assessment scale and Naranjo algorithm.**[32]
- The severity analysis was done using **Hartwig and Siegel scale.**[33]
- The preventability assessment was done using **Modified Schumok and Thorton Scale**.[34]

STATISTICAL ANALYSIS

The data collected were categorically entered in Microsoft excel sheet and was analyzed using SPSS software 2.0 version. Appropriate diagrams and charts were used for pictorial representation of the data. Statistical significance was analyzed using Chi- square test.

RESULTS

Totally 50 patients with DIP were enrolled in the study over the study period of one year.

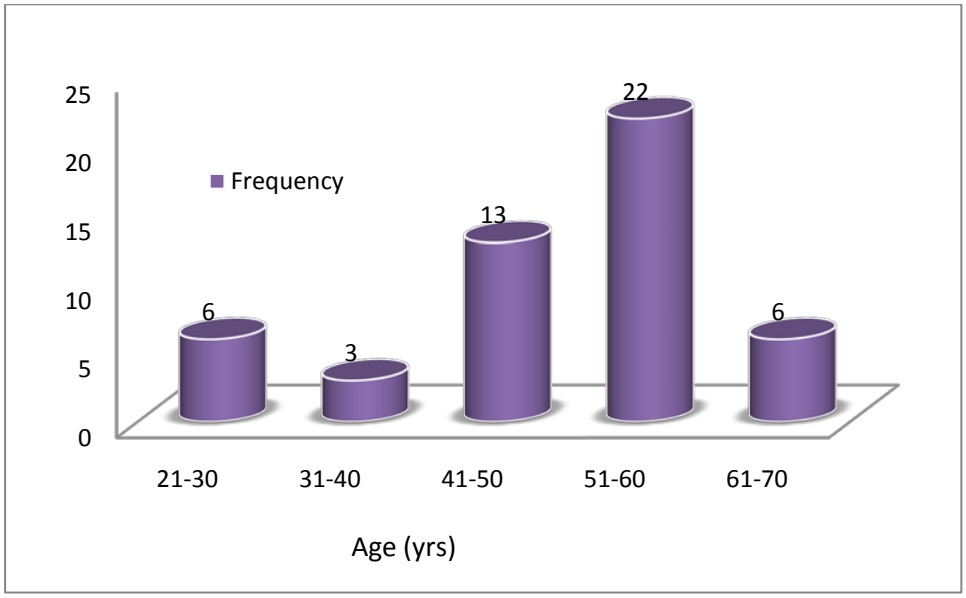
AGE:

Age wise distribution of ADRs in various age groups is shown below.

Table 1: Age wise distribution

Age (yrs)	Frequency	Percent
21-30	6	12.0
31-40	3	6.0
41-50	13	26.0
51-60	22	44.0
61-70	6	12.0
Total	50	100.0

Figure 1: Age wise distribution



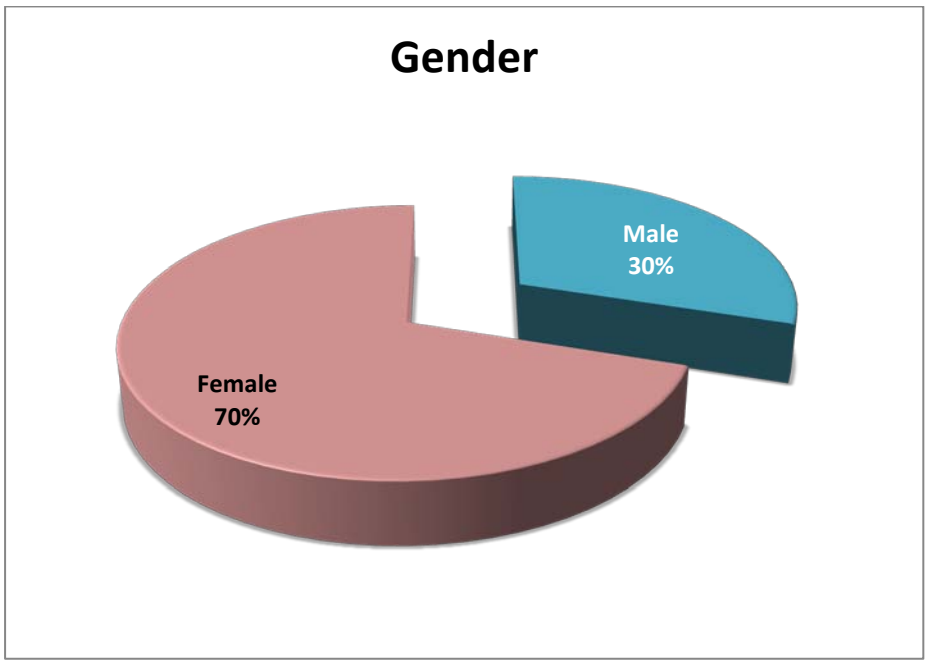
- 44% of ADR was common in the age group of 51-60 yrs. 6% of ADR was seen in the age group of 61-70 yrs.

GENDER:

Table 1: Gender distribution of patients with ADRs

Gender	Frequency	Percent
Male	15	30.0
Female	35	70.0
Total	50	100.0

Figure 2: Gender distribution of patients with ADRs



- DIP was found to be more common in females when compared to males.

PROFILE OF DRUG REACTION

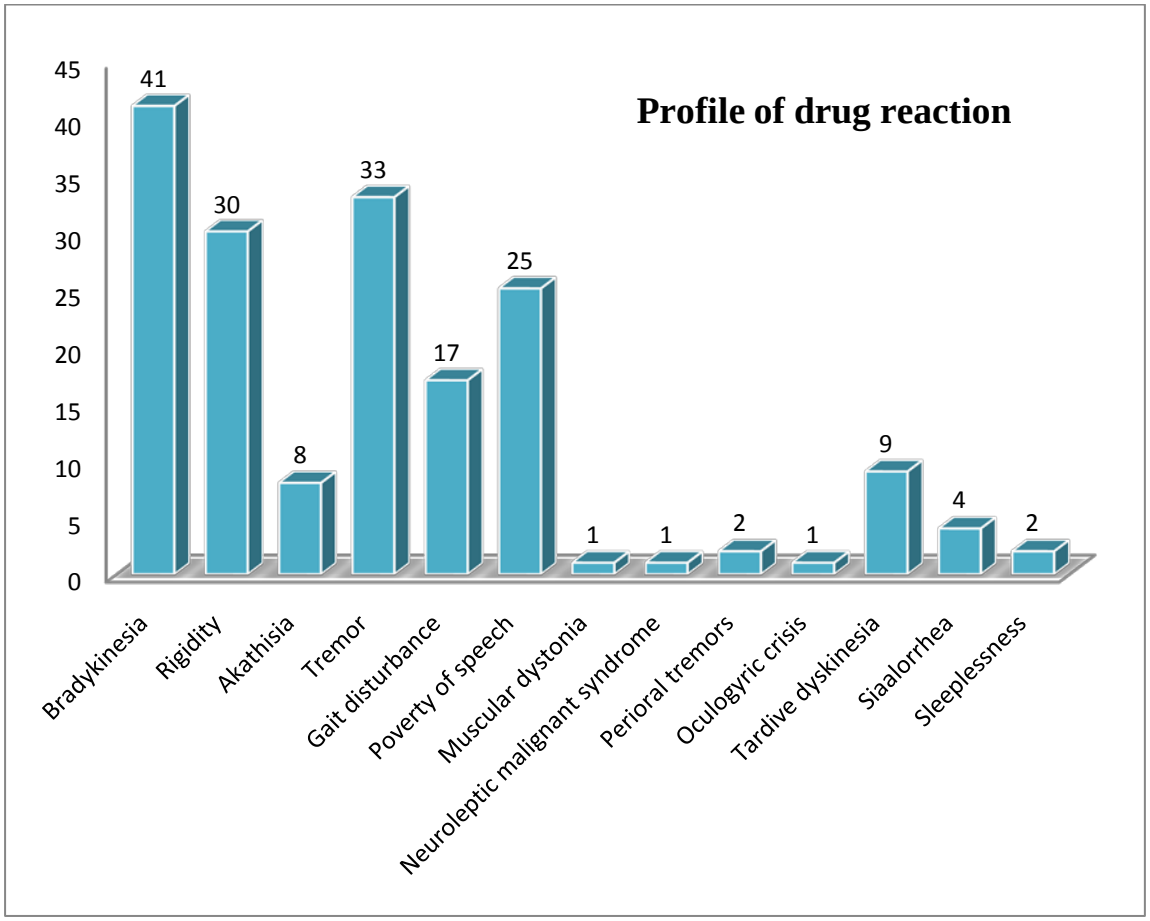
Table 3A: Frequency of different types of drug induced reactions

Profile of drug reaction	Yes		No		Total	
	Count	%	Count	%	Count	%
Bradykinesia	41	82.00	9	18.00	50	100.00
Rigidity	30	60.00	20	40.00	50	100.00
Akathisia	8	16.00	42	84.00	50	100.00
Tremor	33	66.00	17	34.00	50	100.00
Gait disturbance	17	34.00	33	66.00	50	100.00
Poverty of speech	25	50.00	25	50.00	50	100.00
Muscular dystonia	1	2.00	49	98.00	50	100.00
Neuroleptic malignant syndrome	1	2.00	49	98.00	50	100.00
Perioral tremors	2	4.00	48	96.00	50	100.00
Oculogyric crisis	1	2.00	49	98.00	50	100.00
Tardive dyskinesia	9	18.00	41	82.00	50	100.00
Siaalorrhea	4	8.00	46	92.00	50	100.00
Sleeplessness	2	4.00	48	96.00	50	100.00

Table 3B: Distribution of Combinations of Manifestations of DIP:

S.No	Combinations of Manifestations	Number of patients affected	Percentage
1	Bradykinesia + Rigidity	6	12
2	Bradykinesia + Rigidity + Muscular dystonia	1	2
3	Bradykinesia + Rigidity + Akathisia	7	14
4	Bradykinesia + Rigidity + Akathisia + Neuroleptic malignant syndrome	1	2
5	Bradykinesia + Rigidity + Oculogyric crisis	1	2
6	Bradykinesia + Tremor + Poverty of speech + Sialorrhea + Sleeplessness	2	4
7	Gait disturbances + Poverty of speech + Tardive dyskinesia	1	2
8	Tremor + Bradykinesia + Rigidity	5	10
9	Tremor + Bradykinesia + Rigidity + Tardive dyskinesia	1	2
10	Tremor + Bradykinesia + Rigidity + Poverty of speech + Perioral tremors	1	2
11	Tremor + Bradykinesia + Rigidity + Poverty of speech	8	16
12	Tremor + Gait disturbances + Poverty of speech	4	8
13	Tremor + Gait disturbances + Poverty of speech + Tardive dyskinesia	4	8
14	Tremor + Bradykinesia + Gait disturbances + Poverty of speech	5	10
15	Tremor + Bradykinesia + Gait disturbances + Poverty of speech + Tardive dyskinesia	1	2
16	Tremor + Bradykinesia + Gait disturbances + Poverty of speech + Tardive dyskinesia + Sialorrhea	2	4

Figure 3: Frequency of different types of drug induced reactions



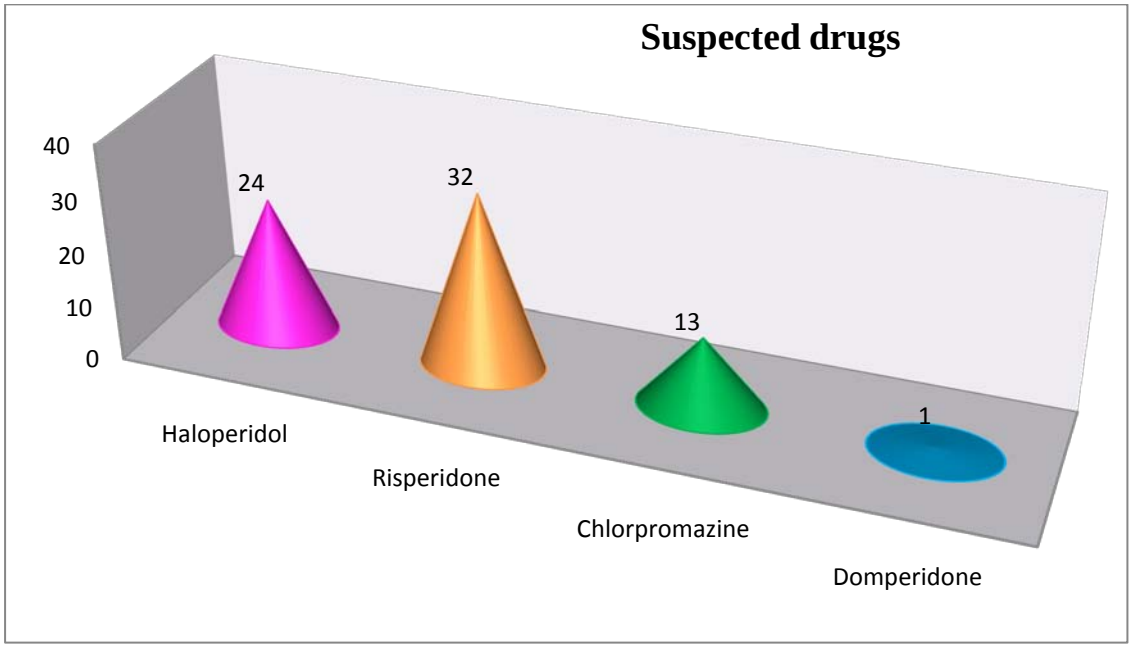
- Most common drug reaction was in the following order, bradykinesia > tremor > rigidity > poverty of speech.
- There were different combinations of drug reactions occurring in the patients.
- More than one reaction occurred in the same patient.

SUSPECTED DRUGS

Table 4A: Frequency of various drugs suspected to be the causative agents

Suspected drug	Frequency	%
Haloperidol	24	48.00
Risperidone	32	64.00
Chlorpromazine	13	26.00
Domperidone	1	2.00

Figure 4A: Frequency of various drugs suspected to be the causative agents

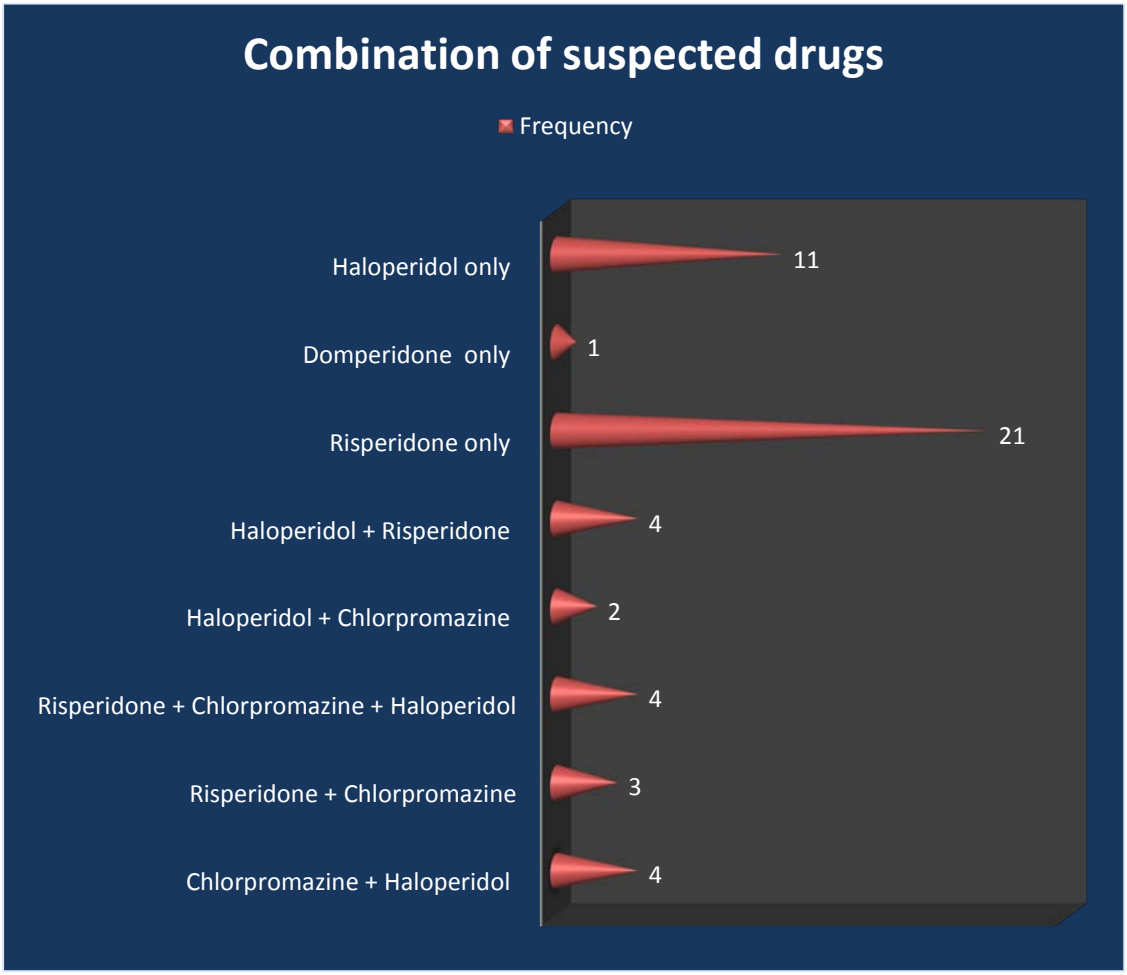


- Most common suspected drug to cause DIP is risperidone followed by haloperidol & chlorpromazine. Domperidone was found to cause DIP, which was considered as new signal.

Table 4B: Distribution of combination of suspected drugs prescribed

S.No	Suspected drugs combination	Frequency	Percentage
1	Chlorpromazine + Haloperidol	4	8
2	Risperidone + Chlorpromazine	3	6
3	Risperidone + Chlorpromazine + Haloperidol	4	8
4	Haloperidol + Chlorpromazine	2	4
5	Haloperidol + Risperidone	4	8
6	Risperidone only	21	42
7	Domperidone only	1	2
8	Haloperidol only	11	22

Figure 4B: Distribution of combination of suspected drugs prescribed



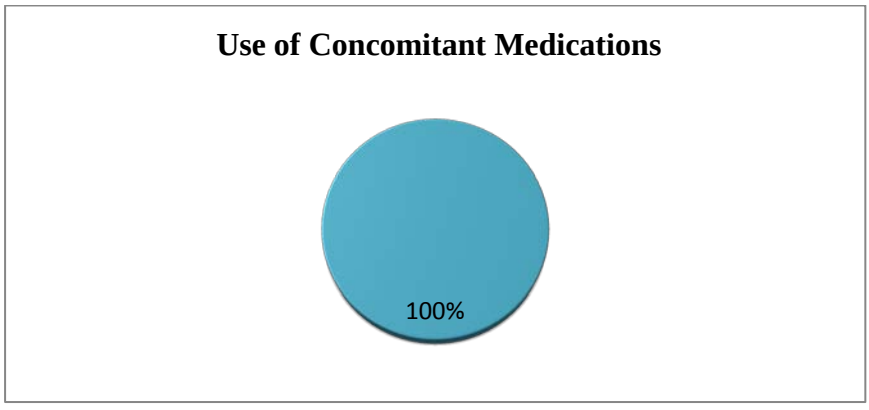
- About 66% of patients were treated with monotherapy (Risperidone, Haloperidol, Domperidone). Whereas 34% of patients were initially prescribed with any one of the above antipsychotics which has lead to the development of DIP, then the drug was discontinued and prescribed with another antipsychotic drug which also was stated to cause DIP.
- Two drugs with the same potential to cause EPS were prescribed to the same patient, even after development of EPS with one drug.

USE OF CONCOMITANT MEDICATIONS

Table 5: Pattern of use of Concomitant Medications

Use of Concomitant Medications	Frequency	Percent
Yes	50	100.0

Figure 5: Pattern of use of Concomitant Medications



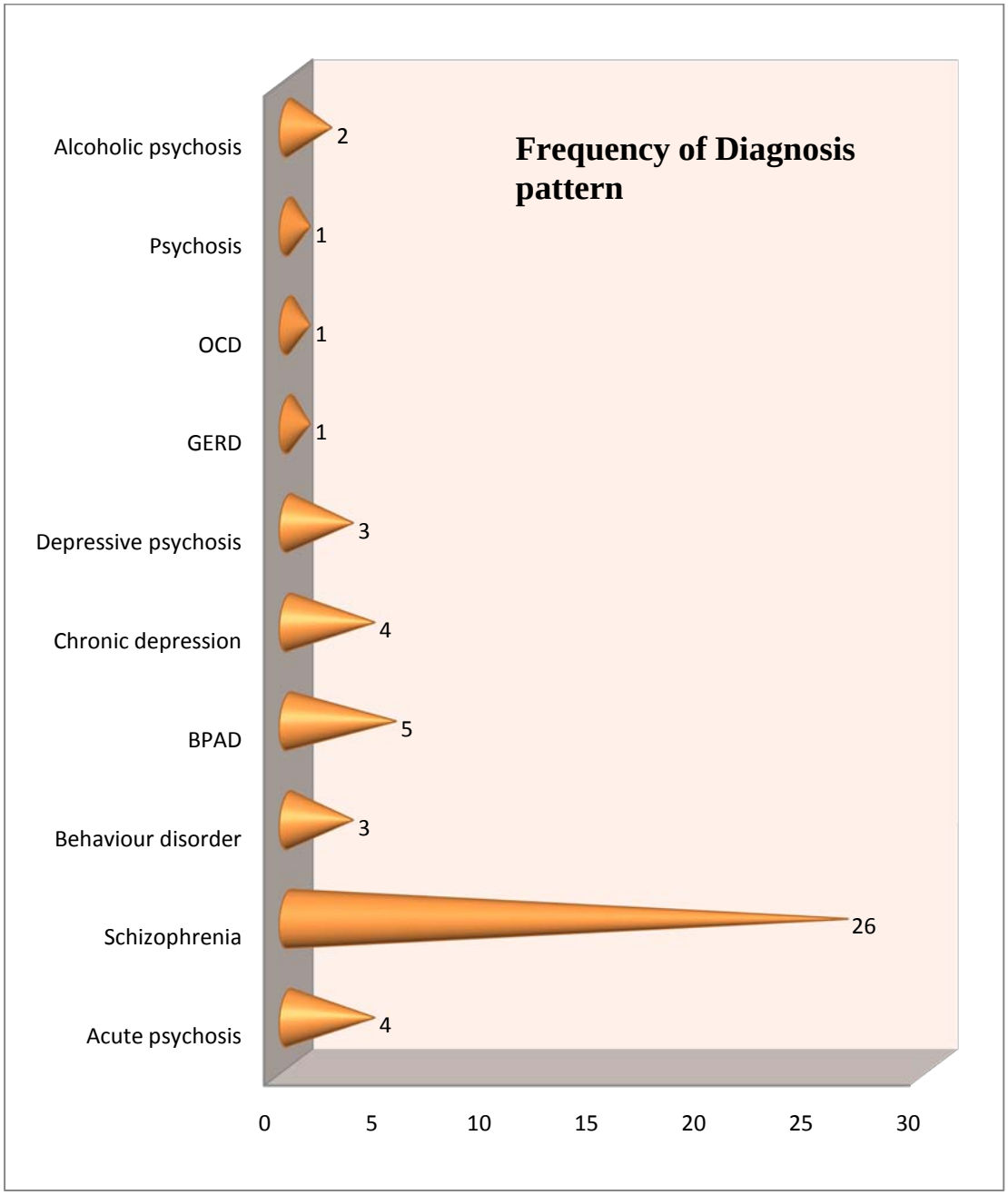
- All the patients were using one or more than one concomitant medications.

DIAGNOSIS

Table 6: Different diagnosis pattern of patient with ADRs

Diagnosis Pattern	Frequency	Percent
Acute psychosis	4	8.0
Schizophrenia	26	52.0
Behaviour disorder	3	6.0
BPAD	5	10.0
Chronic depression	4	8.0
Depressive psychosis	3	6.0
GERD	1	2.0
OCD	1	2.0
Psychosis	1	2.0
Alcoholic psychosis	2	4.0
Total	50	100.0

Figure 6: Different diagnosis pattern of patient with ADRs



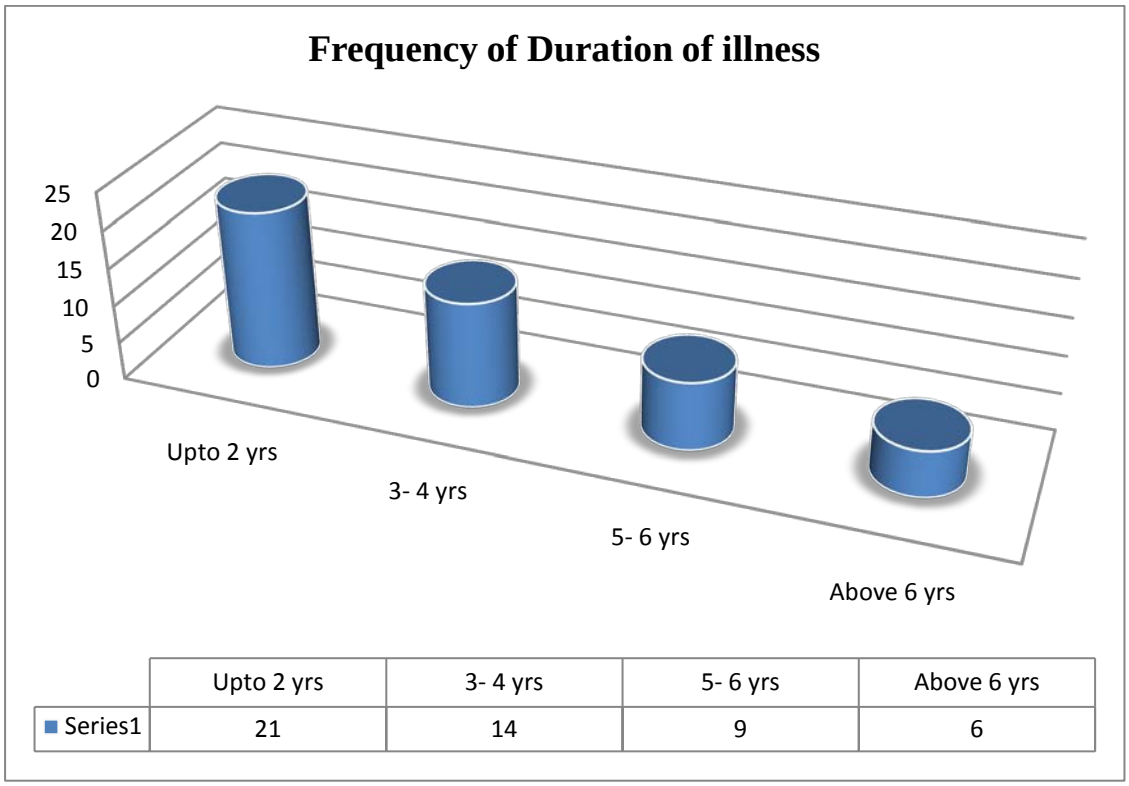
- Most common diagnosis was schizophrenia followed by bipolar affective disorder (BPAD).

DURATION OF ILLNESS

Table 7: Distribution of Duration of illness

Duration of illness (yrs)	Frequency	Percent
Upto 2	21	42.0
3- 4	14	28.0
5- 6	9	18.0
Above 6 – 10	6	12.0
Total	50	100.0

Figure 7: Distribution of Duration of illness



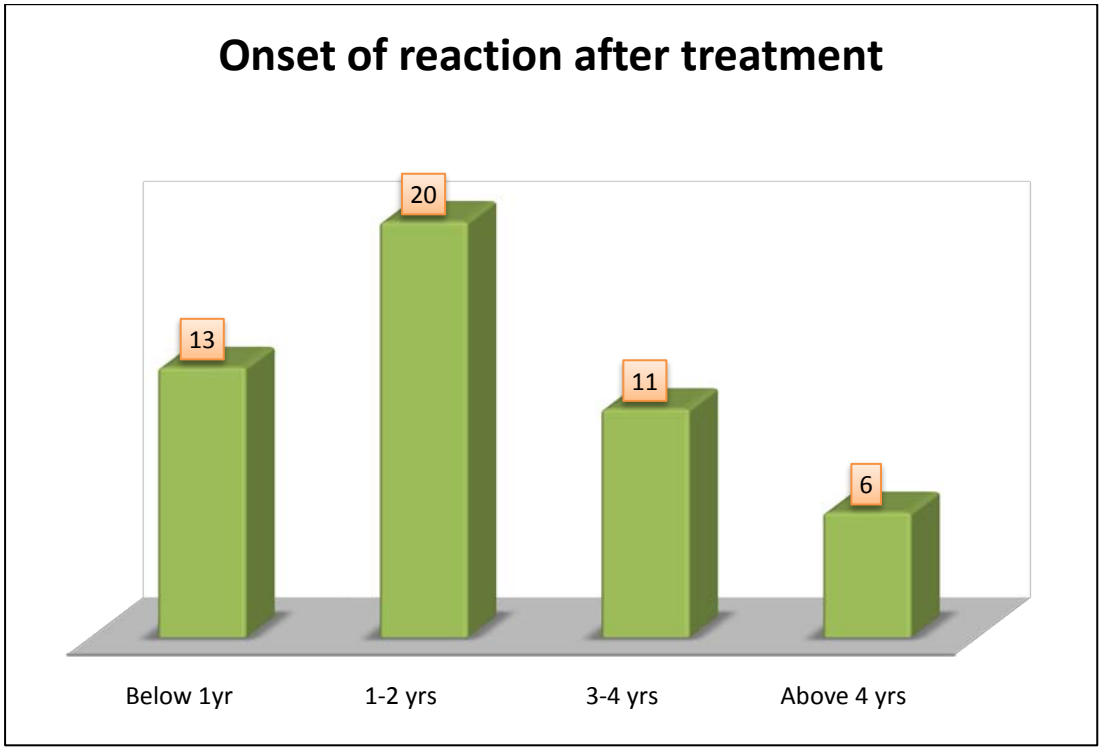
- Duration their diagnosed primary illness varied from 2 years to more than 6 years maximum up to 10 years.

ONSET OF REACTION AFTER TREATMENT

Table 8: Onset of reaction after treatment in years

Onset of reaction after treatment in years	Frequency	Percent
1 month to Below 1year	13	26.0
1-2	20	40.0
3-4	11	22.0
Above 4 - 6	6	12.0
Total	50	100.0

Figure 8: Frequency of Onset of reaction after treatment in years



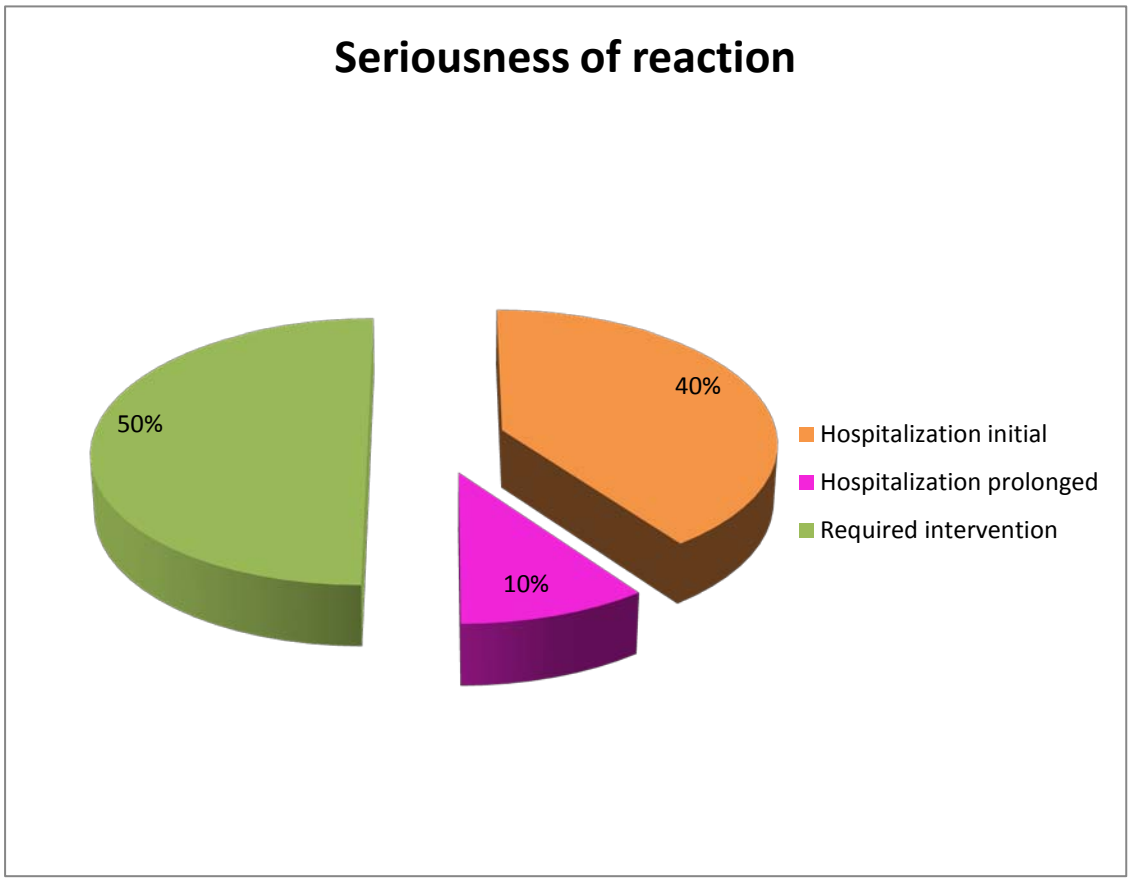
- Most of the patient developed drug reaction after 1to 2yrs of starting the treatment.

SERIOUSNESS OF REACTION

Table 9: Distribution of seriousness of reaction

Seriousness of reaction	Frequency	Percent
Hospitalization initial	20	40.0
Hospitalization prolonged	5	10.0
Required intervention	25	50.0
Total	50	100.0

Figure 9: Distribution of seriousness of reaction



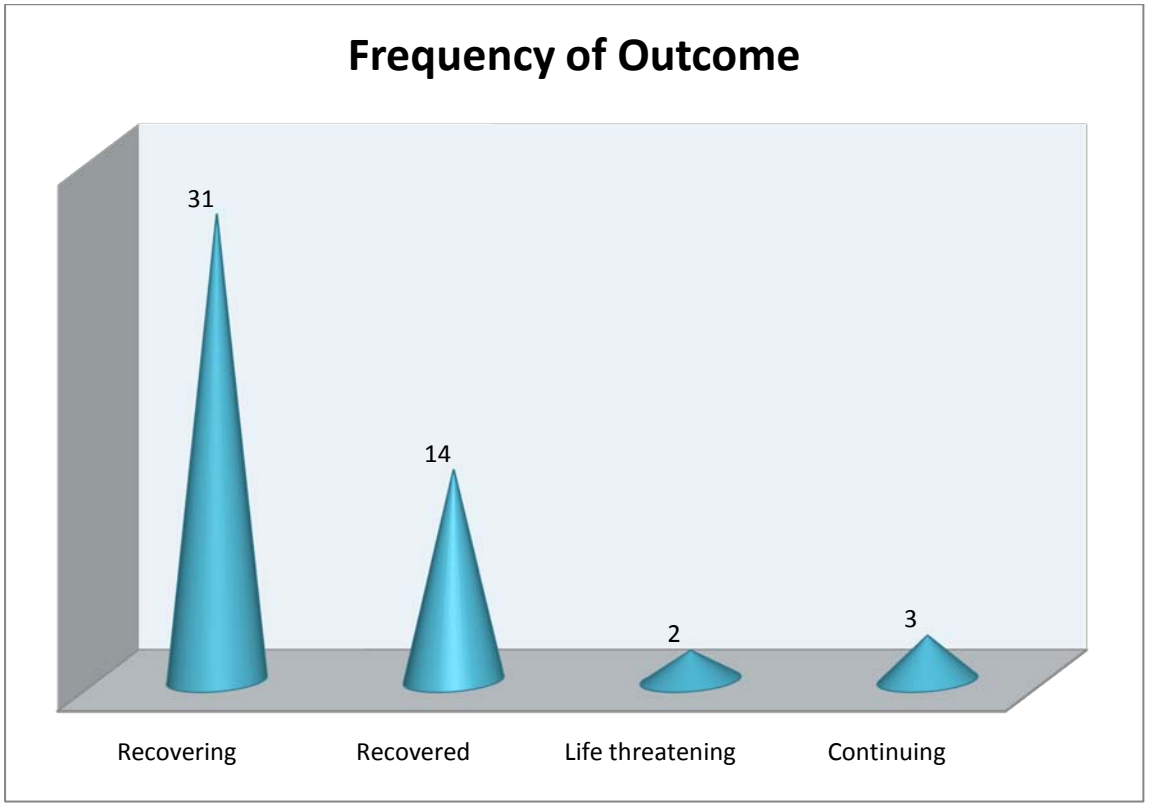
- 25 % 0f cases required intervention to prevent permanent damage due to ADR, 20 % of cases required initial hospitalization & 5 % required prolonged hospitalization due to ADR.

OUTCOME

Table 10: Distribution of outcome

Outcome	Frequency	Percent
Recovering	31	62.0
Recovered	14	28.0
Life threatening	2	4.0
Continuing	3	6.0
Total	50	100.0

Figure 10: Distribution of outcome



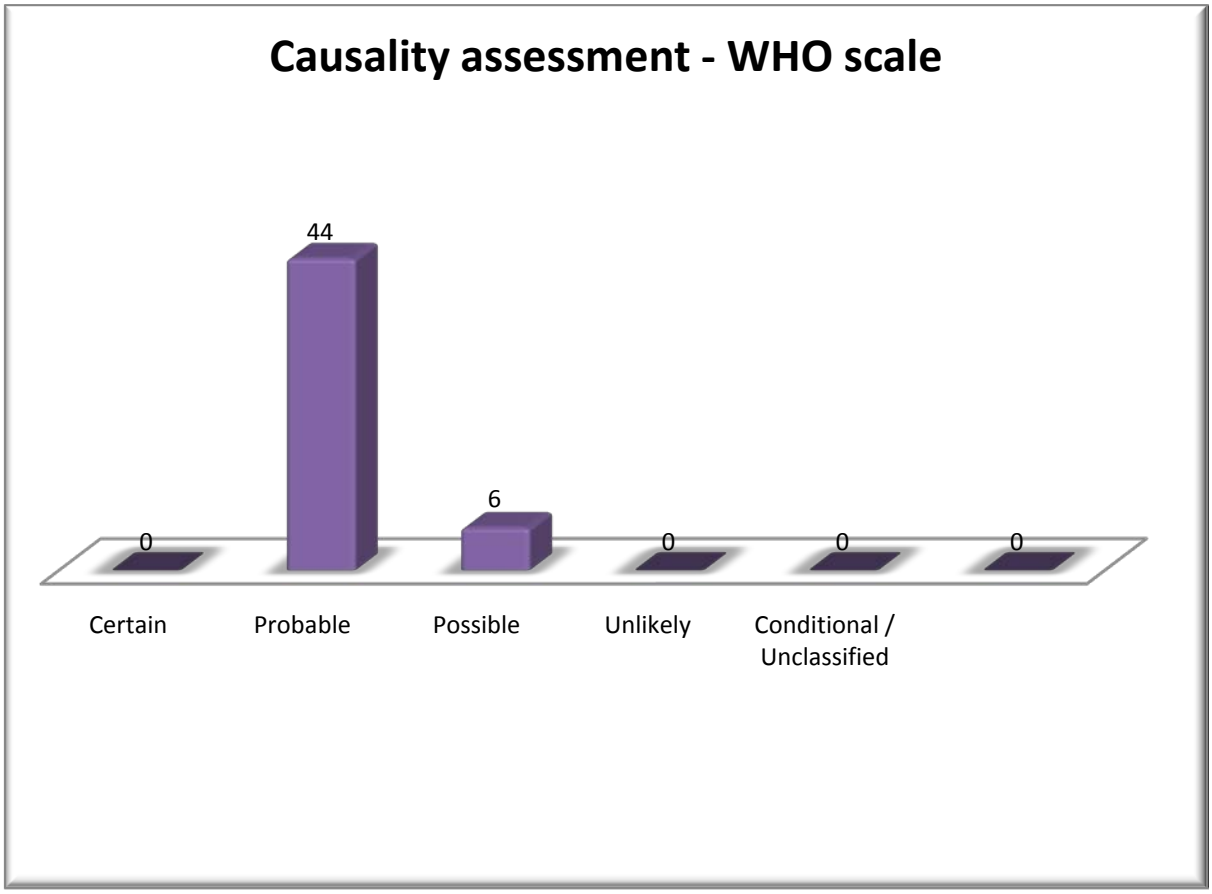
- 31 cases were in recovery phase, 14 cases recovered from ADR, 3 cases were in continuing phase & 2 cases developed serious life threatening ADR.

CAUSALITY ASSESSMENT - WHO SCALE

Table 11: Causality assessment - WHO scale

Causality assessment - WHO scale	Frequency	Percent
Probable	44	88.0
Possible	6	12.0
Total	50	100.0

Figure11: Causality assessment - WHO scale



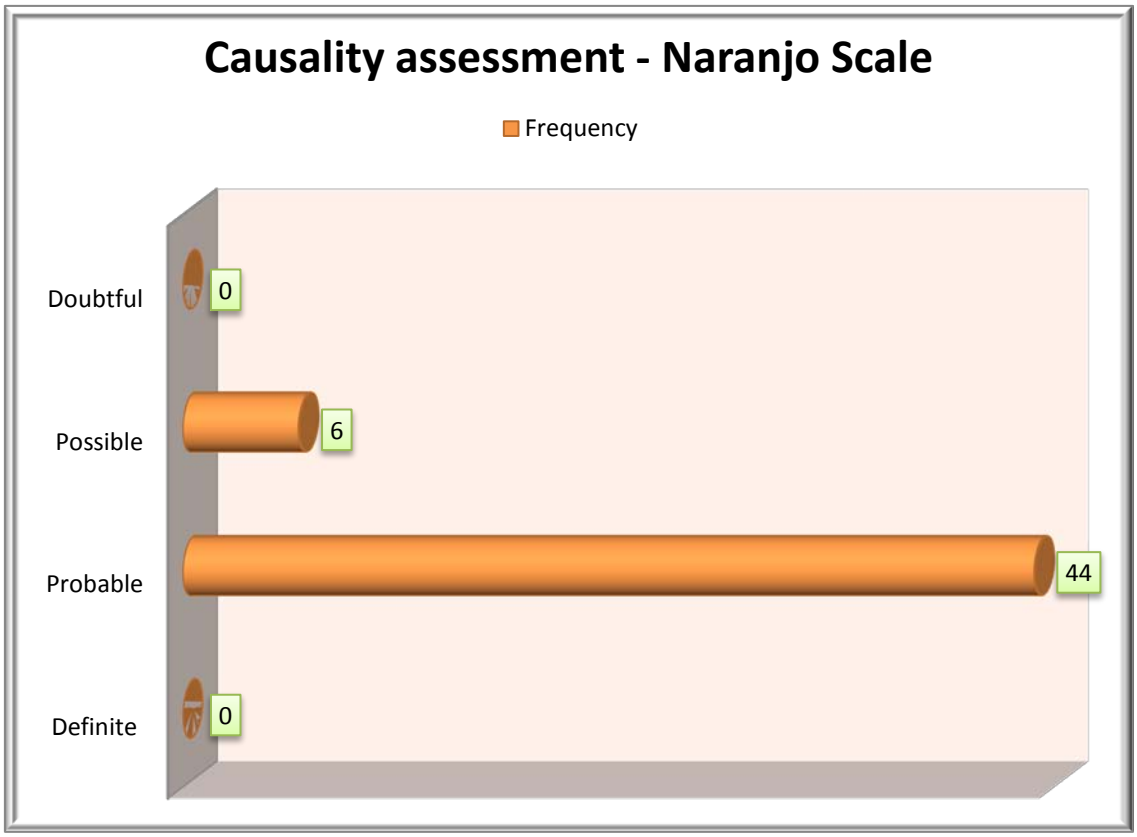
- Maximum ADRs were probable (88%) and rest of them were possible (12%).

CAUSALITY ASSESSMENT – NARANJO SCALE

Table 12: Causality Assessment – Naranjo Scale

Causality Assessment – Naranjo Scale	Frequency	Percent
Definite	0	0
Probable	44	88
Possible	6	12
Doubtful	0	0

Figure 12: Causality Assessment – Naranjo Scale



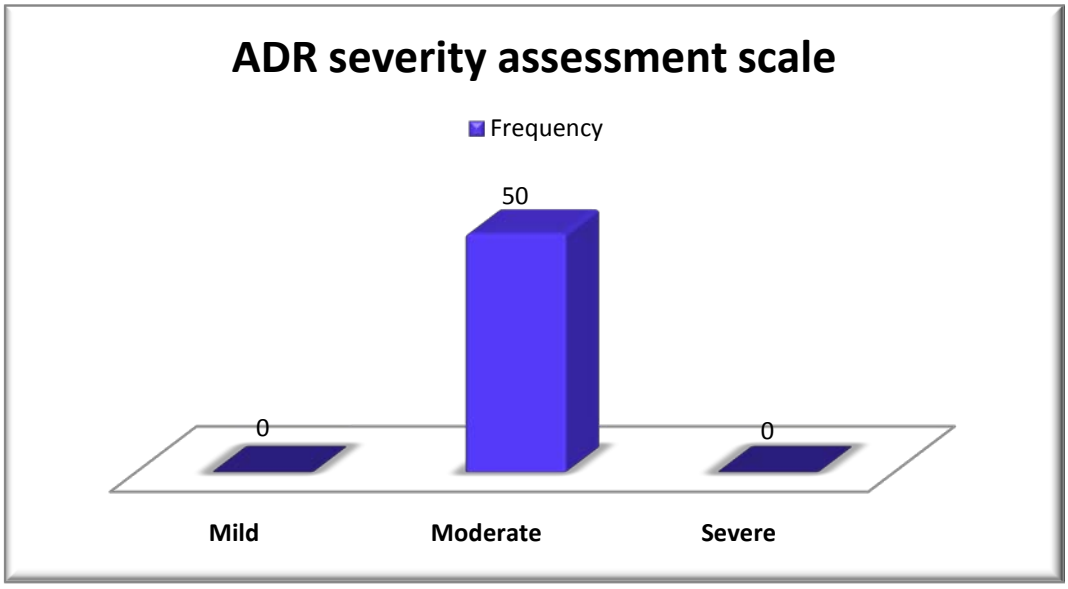
- Maximum ADRs were probable (88%) and rest of them were possible (12%).

ADR SEVERITY ASSESSMENT SCALE

Table 13: ADR severity assessment scale (Modified Hartwig and Siegel scale)

Severity scale	Frequency	Percent
Mild – Level – 1 Level – 2	0	0
Moderate – Level – 3 Level – 4a Level – 4b	50	50
Severe Level - 5 Level – 6 Level - 7	0	0

Figure 13: ADR severity assessment scale (Modified Hartwig and Siegel scale)



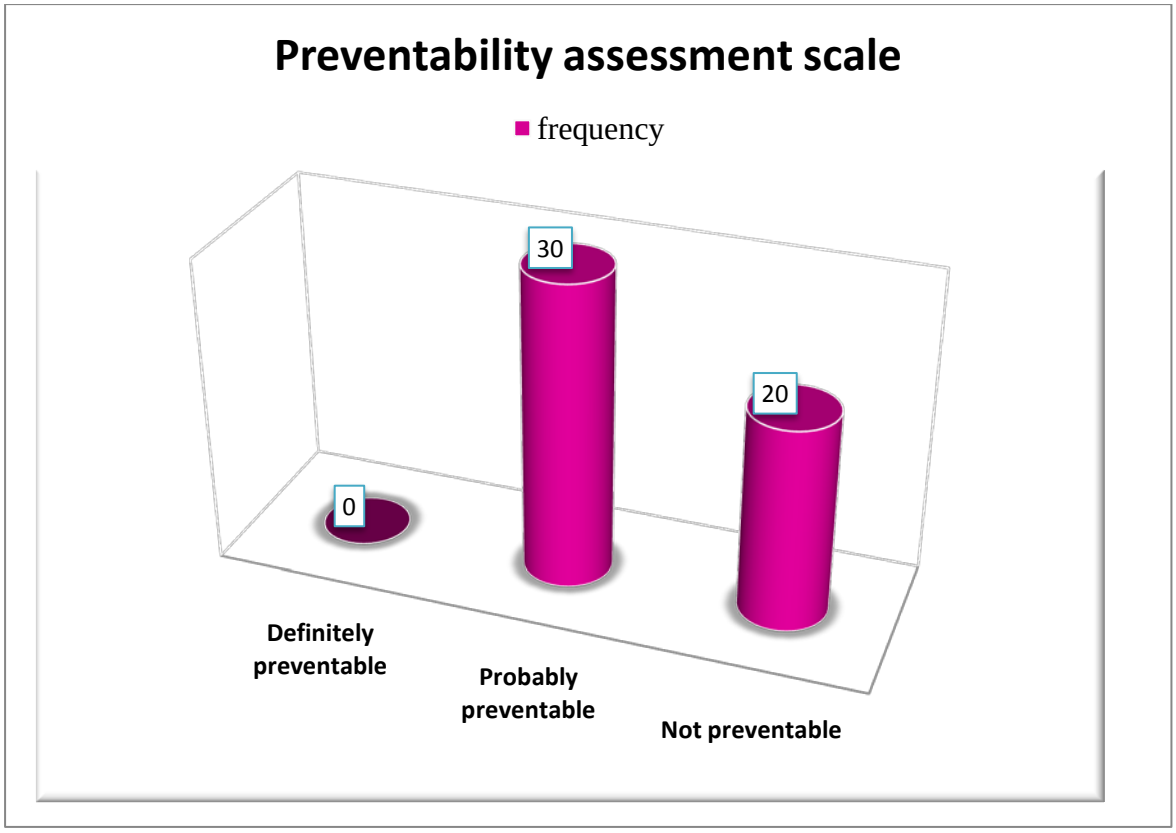
- All the ADRs were of moderately severe requiring dose reduction or discontinuation of the suspected drug and change to another drug.

PREVENTABILITY ASSESSMENT SCALE

Table 14: Preventability Assessment Scale

Preventability Assessment Scale	Frequency	Percent
Definitely preventable	0	0
Probably preventable	30	60.0
Not preventable	20	40.0
Total	50	100.0

Figure 14: Preventability Assessment Scale



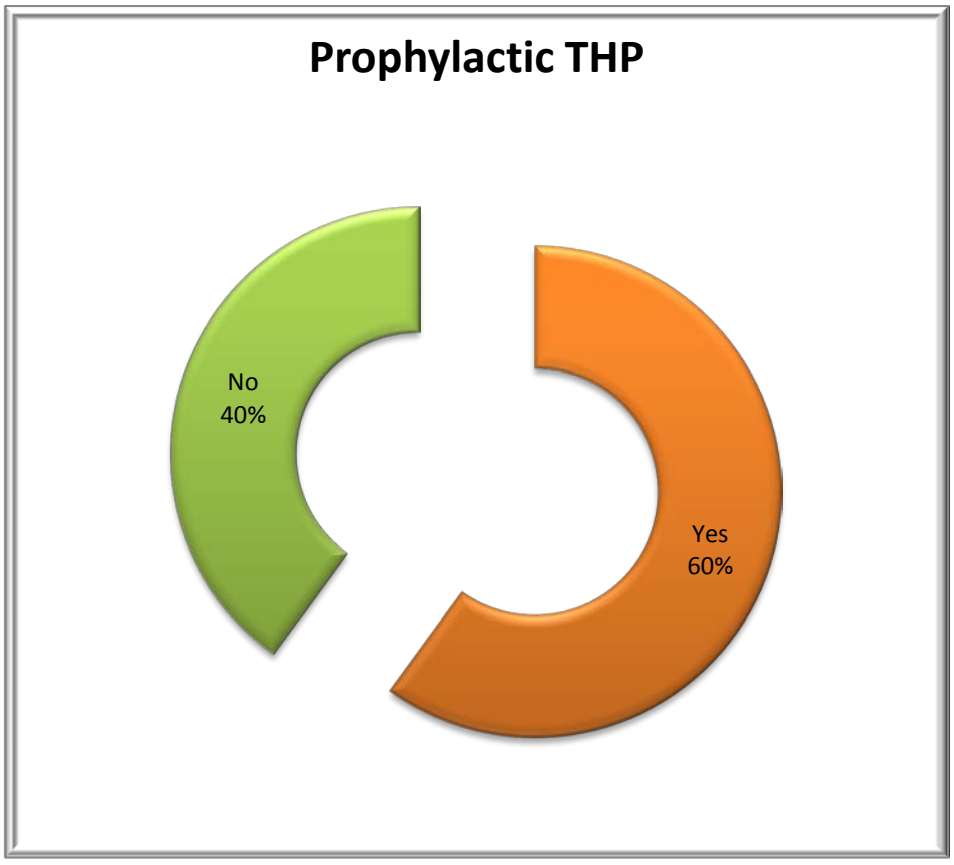
- 60 % of ADRs were probably preventable & 40 % were not preventable.

PROPHYLACTIC TREATMENT WITH THP

Table 15: Prophylactic treatment with THP

Prophylactic treatment with THP	Frequency	Percent
Yes	30	60.0
No	20	40.0
Total	50	100.0

Figure 15: Prophylactic treatment with THP



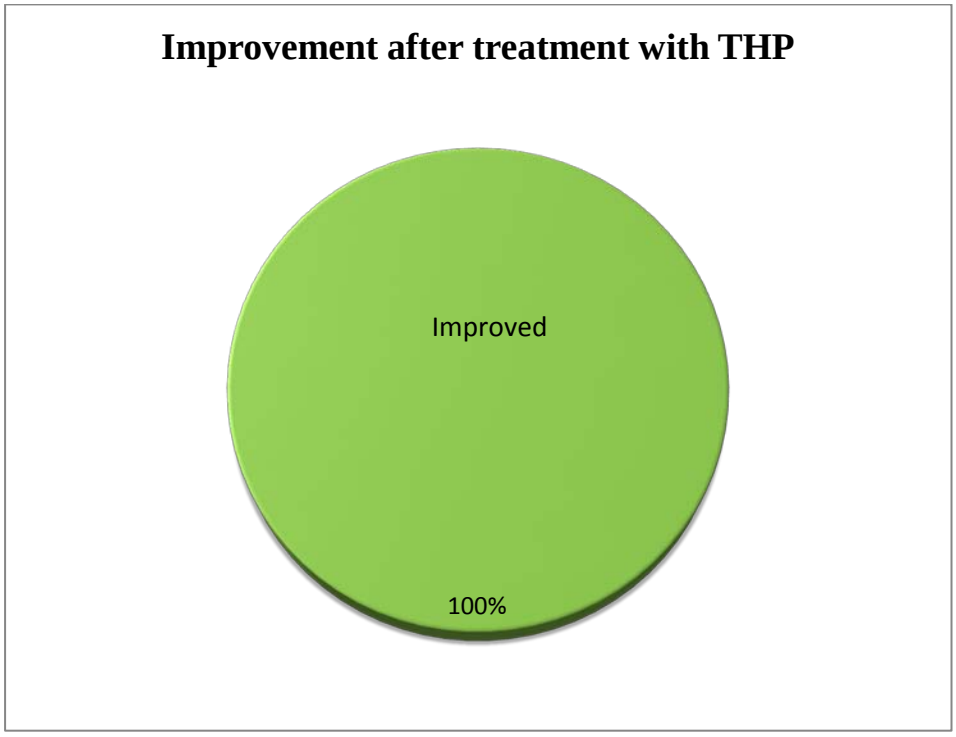
- 60% of patients were prophylactically treated with THP

IMPROVEMENT AFTER TREATMENT WITH THP

Table 16: Improvement after treatment with THP

Improvement after treatment with THP	Frequency	Percent
Yes	50	100.0

Figure 16: Improvement after treatment with THP



- The entire patients with ADRs improved after treatment with THP.

AGE VERSUS SERIOUSNESS OF REACTION

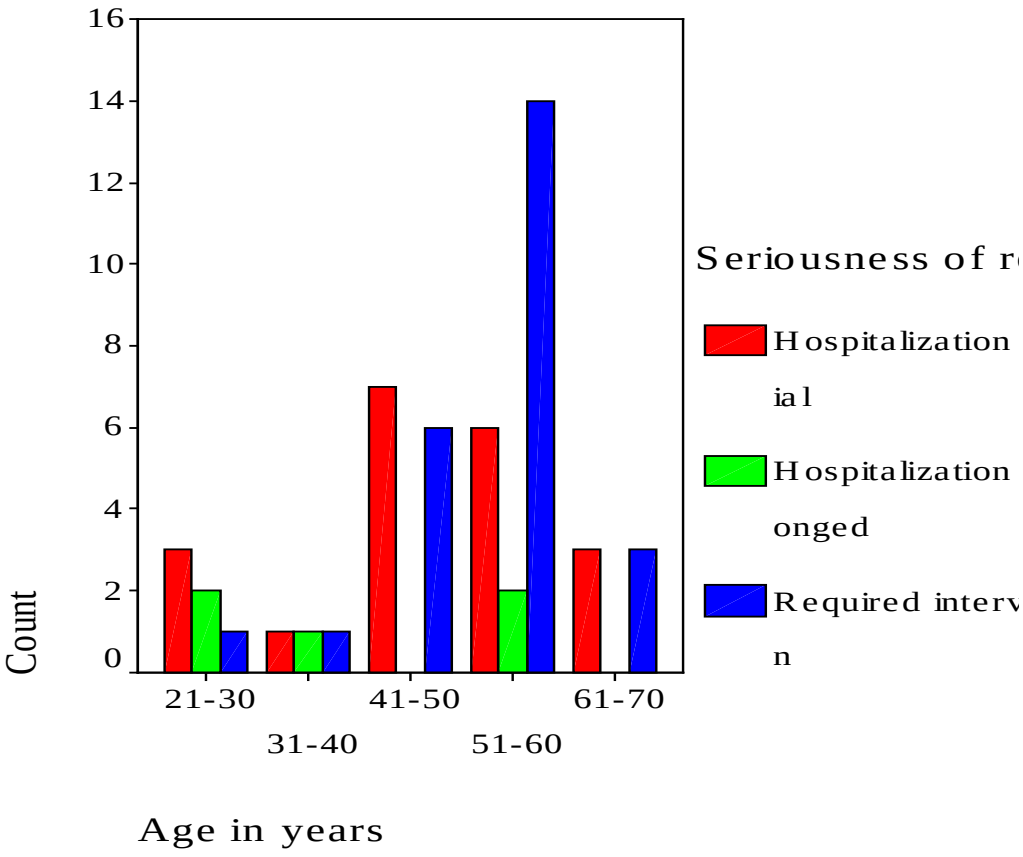
Table 17: Age versus Seriousness of Reaction

			Seriousness of reaction			Total
			Hospitalization initial	Hospitalization prolonged	Required intervention	
Age in years	21-30	Count	3	2	1	6
		% within Age in years	50.0%	33.3%	16.7%	100.0%
		% within Seriousness of reaction	15.0%	40.0%	4.0%	12.0%
	31-40	Count	1	1	1	3
		% within Age in years	33.3%	33.3%	33.3%	100.0%
		% within Seriousness of reaction	5.0%	20.0%	4.0%	6.0%
	41-50	Count	7	0	6	13
		% within Age in years	53.8%	.0%	46.2%	100.0%
		% within Seriousness of reaction	35.0%	.0%	24.0%	26.0%
	51-60	Count	6	2	14	22
		% within Age in years	27.3%	9.1%	63.6%	100.0%
		% within Seriousness of reaction	30.0%	40.0%	56.0%	44.0%
	61-70	Count	3	0	3	6
		% within Age in years	50.0%	.0%	50.0%	100.0%
		% within Seriousness of reaction	15.0%	.0%	12.0%	12.0%
Total		Count	20	5	25	50
		% within Age in years	40.0%	10.0%	50.0%	100.0%
		% within Seriousness of reaction	100.0%	100.0%	100.0%	100.0%

Chi-Square Tests

	Value	df	Asymp. Sig. (2-sided)
Pearson Chi-Square	11.022(a)	8	.200
Likelihood Ratio	11.505	8	.175
Linear-by-Linear Association	1.708	1	.191
N of Valid Cases	50		

Figure 17: Age versus Seriousness of Reaction



- All ADRs required various interventions in all age groups.

AGE VERSUS OUTCOME OF ADR

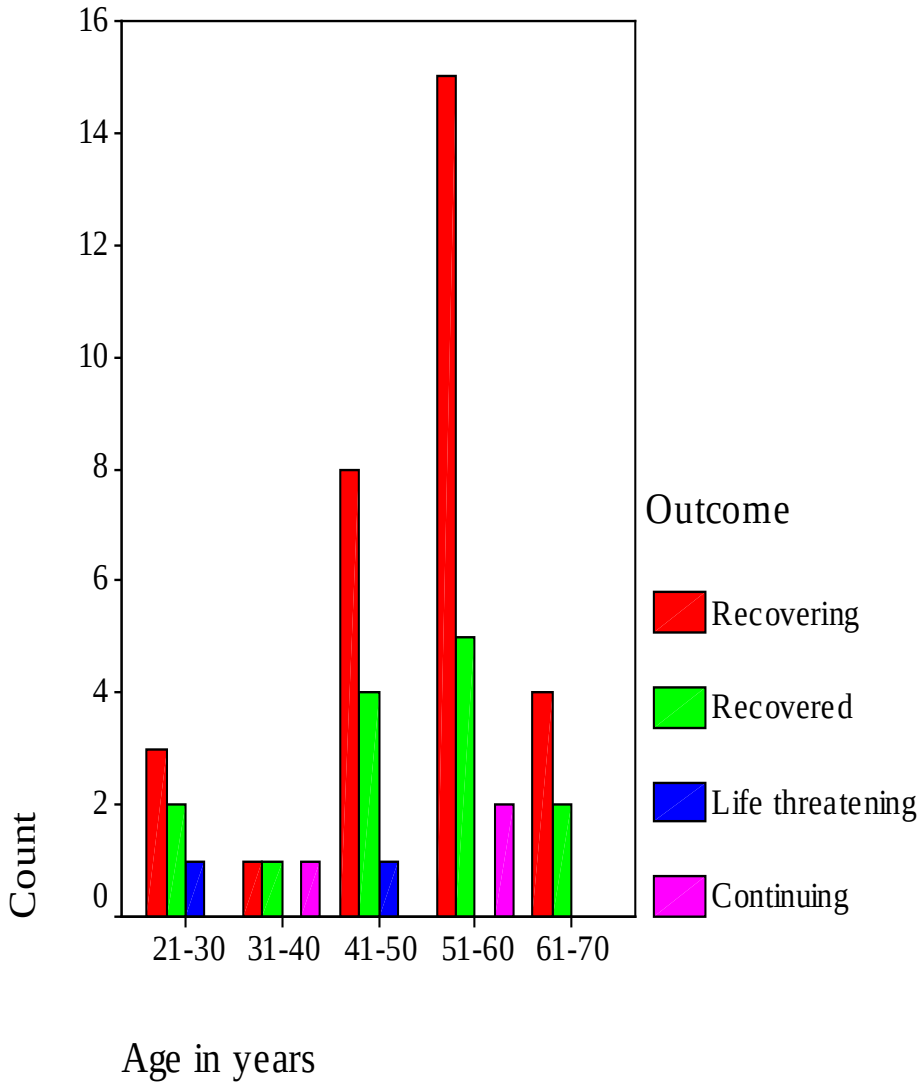
Table 18: Distribution of Outcome of ADR in different age groups

			Outcome				Total
			Recovering	Recovered	Life threatening	Continuing	
Age in years	21-30	Count	3	2	1	0	6
		% within Age in years	50.0%	33.3%	16.7%	.0%	100.0 %
		% within Outcome	9.7%	14.3%	50.0%	.0%	12.0 %
	31-40	Count	1	1	0	1	3
		% within Age in years	33.3%	33.3%	.0%	33.3%	100.0 %
		% within Outcome	3.2%	7.1%	.0%	33.3%	6.0%
	41-50	Count	8	4	1	0	13
		% within Age in years	61.5%	30.8%	7.7%	.0%	100.0 %
		% within Outcome	25.8%	28.6%	50.0%	.0%	26.0 %
	51-60	Count	15	5	0	2	22
		% within Age in years	68.2%	22.7%	.0%	9.1%	100.0 %
		% within Outcome	48.4%	35.7%	.0%	66.7%	44.0 %
	61-70	Count	4	2	0	0	6
		% within Age in years	66.7%	33.3%	.0%	.0%	100.0 %
		% within Outcome	12.9%	14.3%	.0%	.0%	12.0 %
Total		Count	31	14	2	3	50
		% within Age in years	62.0%	28.0%	4.0%	6.0%	100.0 %
		% within Outcome	100.0%	100.0%	100.0%	100.0%	100.0 %

Chi-Square Tests

	Value	df	Asymp. Sig. (2-sided)
Pearson Chi-Square	10.776(a)	12	.548
Likelihood Ratio	10.446	12	.577
Linear-by-Linear Association	1.141	1	.286
N of Valid Cases	50		

Figure 18: Distribution of Outcome of ADR in different age groups



- Most of the patients in all age groups were in recovery phase especially more in the age group ranging from 51-60 yrs. Very few patients recovered. There is no significance between age groups and outcome as the P value = .548

GENDER VERSUS SERIOUSNESS OF REACTION

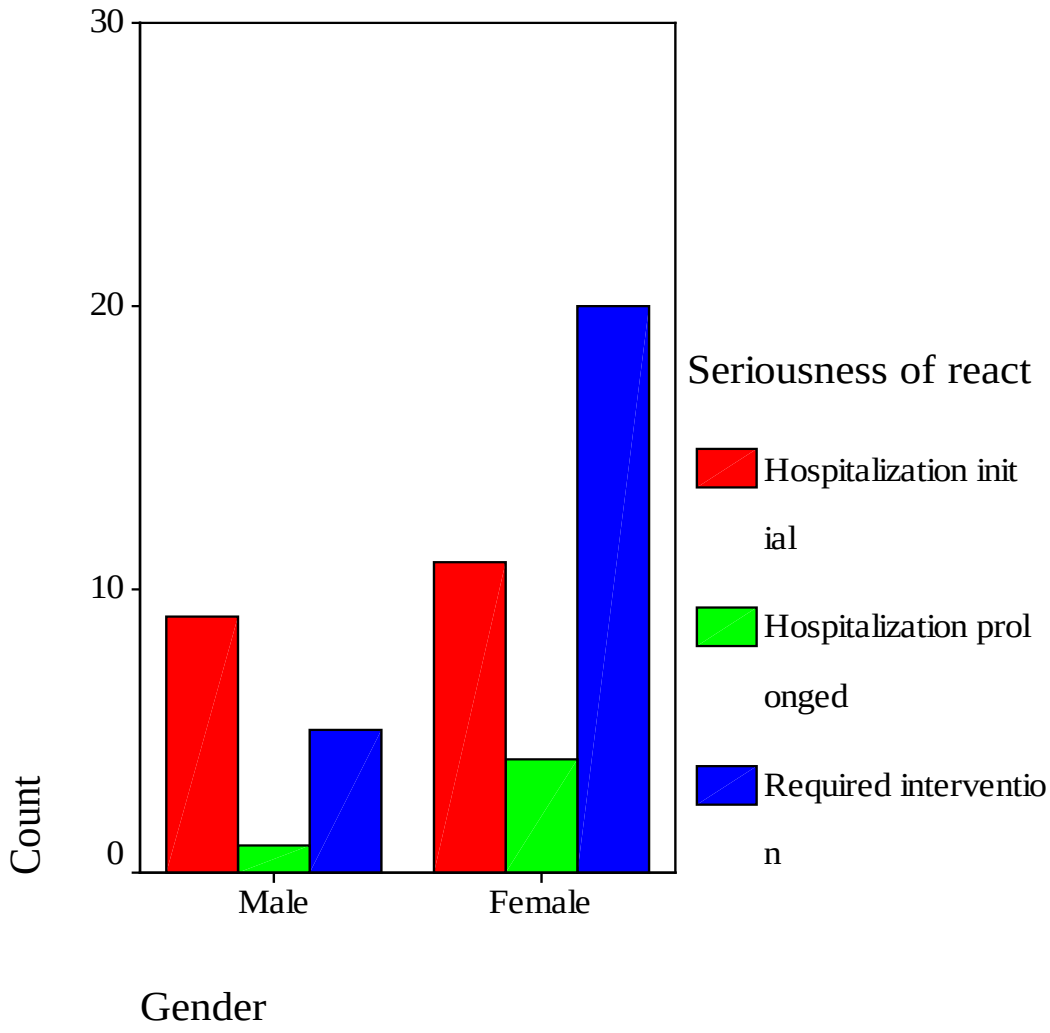
Table 19: Distribution of Gender versus Seriousness of reaction

			Seriousness of reaction			Total
			Hospitalization initial	Hospitalization prolonged	Required intervention	
Gender	Male	Count	9	1	5	15
		% within Gender	60.0%	6.7%	33.3%	100.0%
		% within Seriousness of reaction	45.0%	20.0%	20.0%	30.0%
	Female	Count	11	4	20	35
		% within Gender	31.4%	11.4%	57.1%	100.0%
		% within Seriousness of reaction	55.0%	80.0%	80.0%	70.0%
Total		Count	20	5	25	50
		% within Gender	40.0%	10.0%	50.0%	100.0%
		% within Seriousness of reaction	100.0%	100.0%	100.0%	100.0%

Chi-Square Tests

	Value	df	Asymp. Sig. (2-sided)
Pearson Chi-Square	3.571(a)	2	.168
Likelihood Ratio	3.537	2	.171
Linear-by-Linear Association	3.172	1	.075
N of Valid Cases	50		

Figure 19: Distribution of Gender versus Seriousness of reaction



- The distribution of seriousness of reaction was different among male and female patient. Female patients required more intervention and hospitalization than male patients. But there is no statistical significant difference found between sex and seriousness of reaction when Chi-square test is applied as the P value is .168

GENDER VERSUS OUTCOME OF ADR

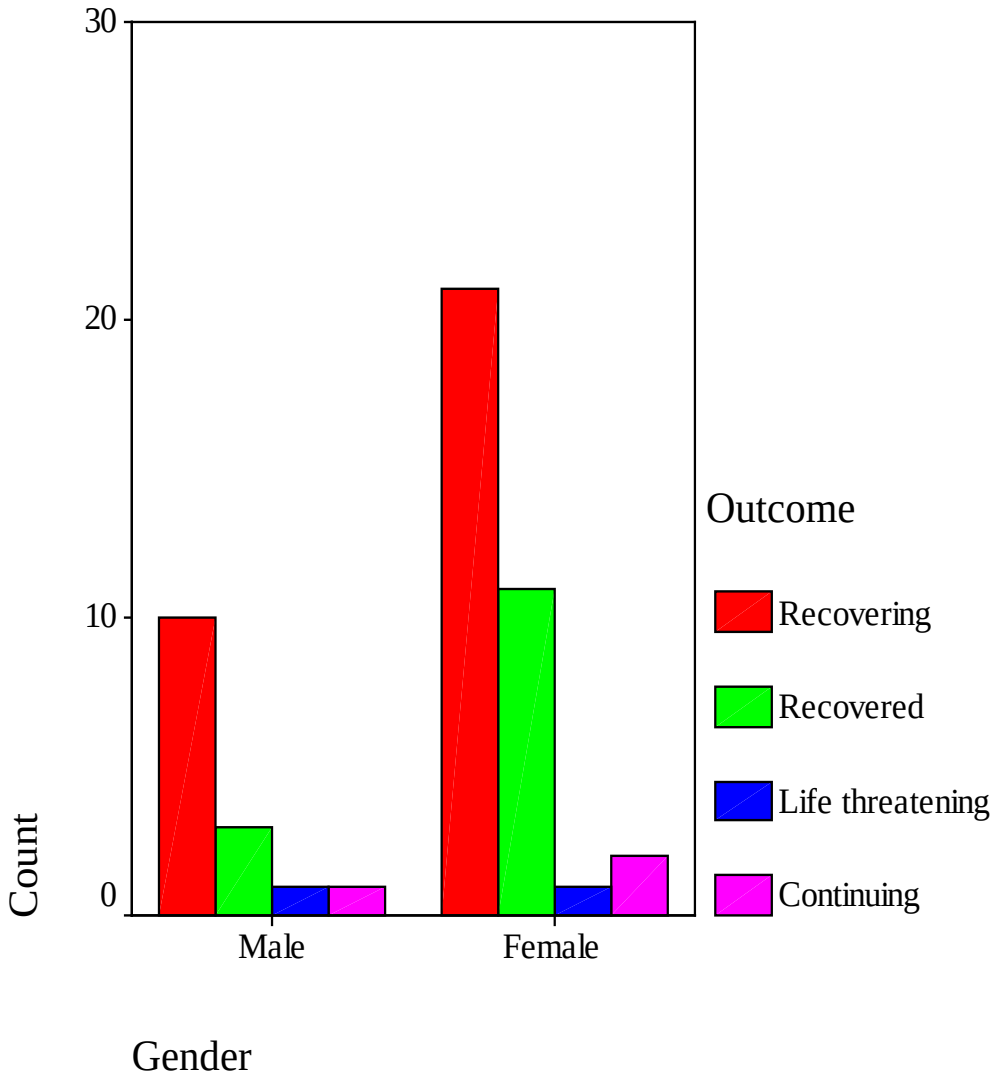
Table 20: Distribution of Gender versus Outcome of ADR

			Outcome				Total
			Recovering	Recovered	Life threatening	Continuing	
Gender	Male	Count	10	3	1	1	15
		% within Gender	66.7%	20.0%	6.7%	6.7%	100.0%
		% within Outcome	32.3%	21.4%	50.0%	33.3%	30.0%
	Female	Count	21	11	1	2	35
		% within Gender	60.0%	31.4%	2.9%	5.7%	100.0%
		% within Outcome	67.7%	78.6%	50.0%	66.7%	70.0%
Total		Count	31	14	2	3	50
		% within Gender	62.0%	28.0%	4.0%	6.0%	100.0%
		% within Outcome	100.0%	100.0%	100.0%	100.0%	100.0%

Chi-Square Tests

	Value	df	Asymp. Sig. (2-sided)
Pearson Chi-Square	.962(a)	3	.810
Likelihood Ratio	.961	3	.811
Linear-by-Linear Association	.001	1	.971
N of Valid Cases	50		

Figure 20: Distribution of Gender versus Outcome of ADR



- The distribution of gender versus outcome varies among male and female patients. Female patients showed better outcome when compared with male patients. But there is no significant difference found between gender and outcome of ADR when Chi-square test is applied as the P value is .810

PROPHYLACTIC THP VERSUS OUTCOME

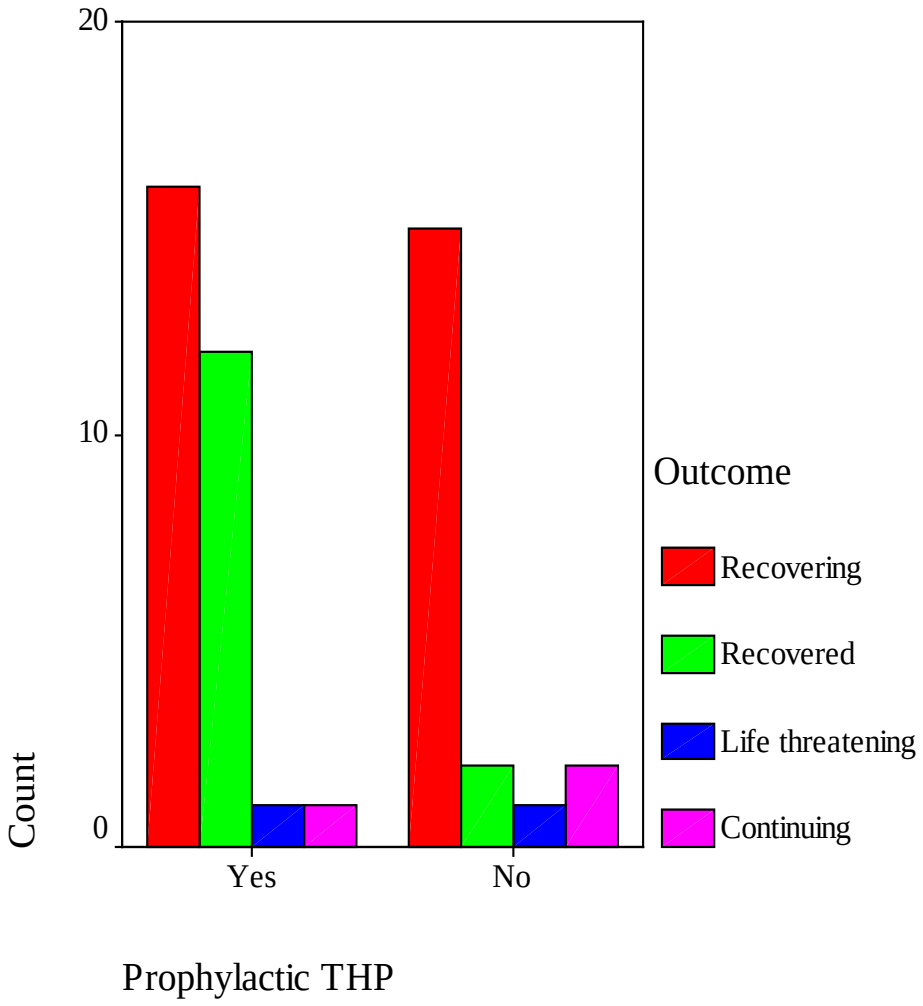
Table 21: Distribution of Prophylactic THP versus Outcome

			Outcome				Total
			Recovering	Recovered	Life threatening	Continuing	
Prophylactic THP	Yes	Count	16	12	1	1	30
		% within Prophylactic THP	53.3%	40.0%	3.3%	3.3%	100.0%
		% within Outcome	51.6%	85.7%	50.0%	33.3%	60.0%
	No	Count	15	2	1	2	20
		% within Prophylactic THP	75.0%	10.0%	5.0%	10.0%	100.0%
		% within Outcome	48.4%	14.3%	50.0%	66.7%	40.0%
Total		Count	31	14	2	3	50
		% within Prophylactic THP	62.0%	28.0%	4.0%	6.0%	100.0%
		% within Outcome	100.0%	100.0%	100.0%	100.0%	100.0%

Chi-Square Tests

	Value	df	Asymp. Sig. (2-sided)
Pearson Chi-Square	5.738(a)	3	.125
Likelihood Ratio	6.283	3	.099
Linear-by-Linear Association	.076	1	.783
N of Valid Cases	50		

Figure 21: Distribution of Prophylactic THP versus Outcome



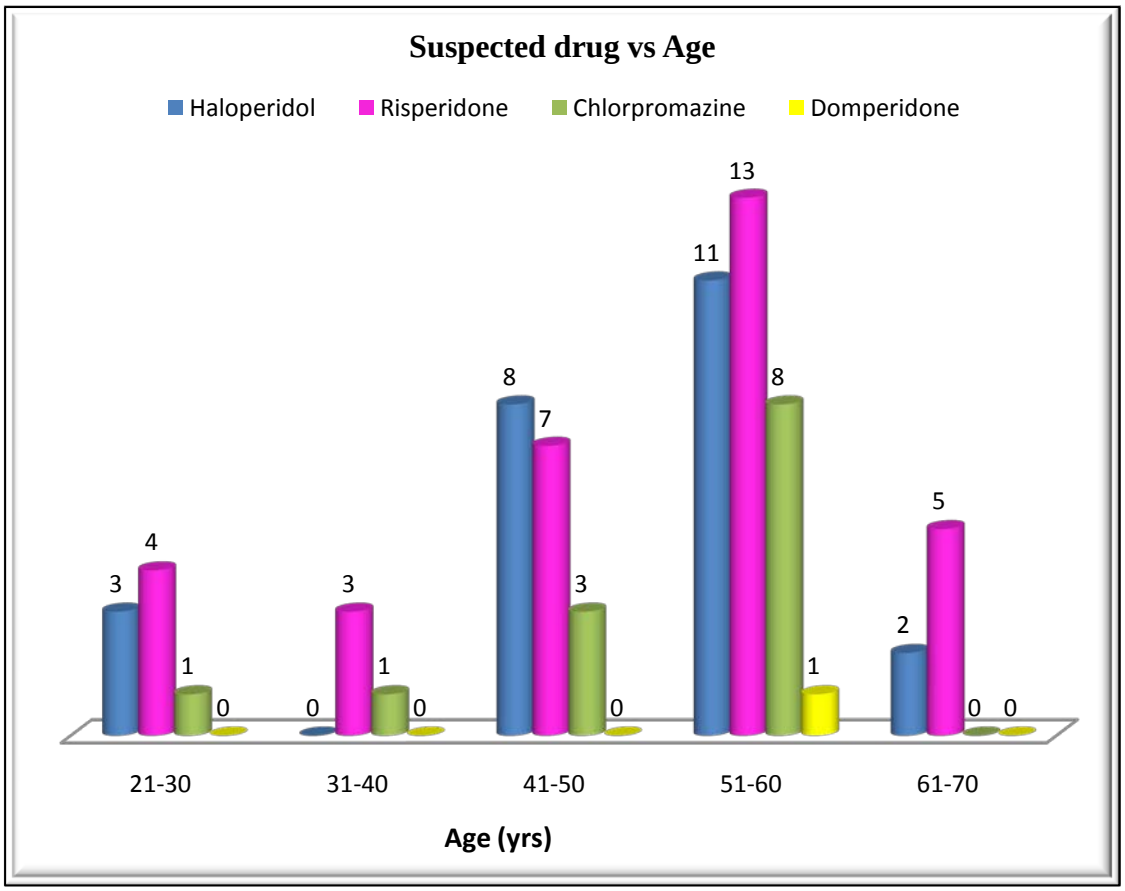
- The outcome of ADR was slightly better when the patients were prophylactically treated with THP. The recovery from ADR was found to more when patients were prescribed with prophylactic THP. But there is no significant difference found between gender and outcome of ADR when Chi-square test is applied as the P value is .810

SUSPECTED DRUGS VERSUS AGE

Table 22: Distribution of Suspected drugs versus age

Suspected drugs	Age in years					Total
	21-30	31-40	41-50	51-60	61-70	
Haloperidol	3	0	8	11	2	24
Risperidone	4	3	7	13	5	32
Chlorpromazine	1	1	3	8	0	13
Domperidone	0	0	0	1	0	1

Figure 22: Distribution of Suspected drugs versus age



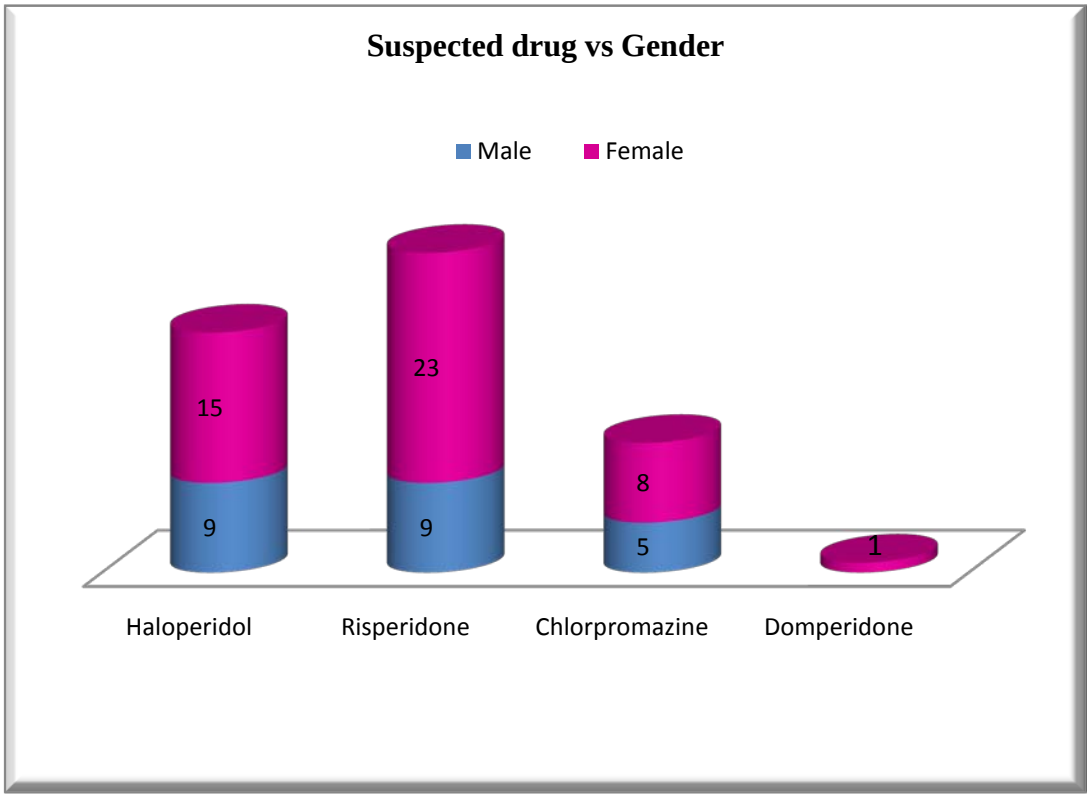
- Suspected drugs were more commonly used in age group of 51-60 years and least commonly used in age group of 31-40 years.

SUSPECTED DRUG VERSUS GENDER

Table 23: Distribution of Suspected Drug versus Gender

Suspected drugs	Gender		Total
	Male	Female	
Haloperidol	9	15	24
Risperidone	9	23	32
Chlorpromazine	5	8	13
Domperidone	0	1	1

Figure 23: Distribution of Suspected Drug versus Gender



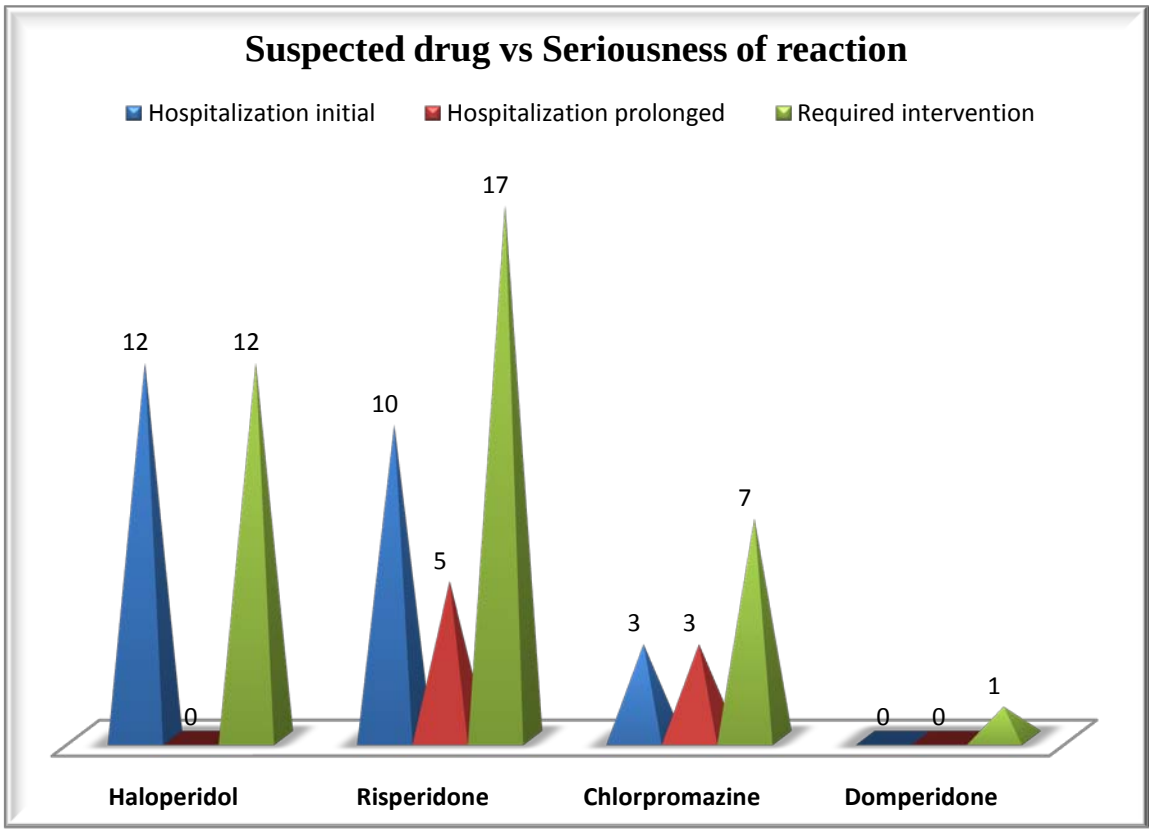
- All the suspected drugs were more commonly used by female patients when compared with male patients.

SUSPECTED DRUG VERSUS SERIOUSNESS OF REACTION

Table 24: Distribution of Suspected Drug versus Seriousness of Reaction

Suspected drugs	Seriousness of reaction			Total
	Hospitalization initial	Hospitalization prolonged	Required intervention	
Haloperidol	12	0	12	24
Risperidone	10	5	17	32
Chlorpromazine	3	3	7	13
Domperidone	0	0	1	1

Figure 24: Distribution of Suspected Drug versus Seriousness of Reaction



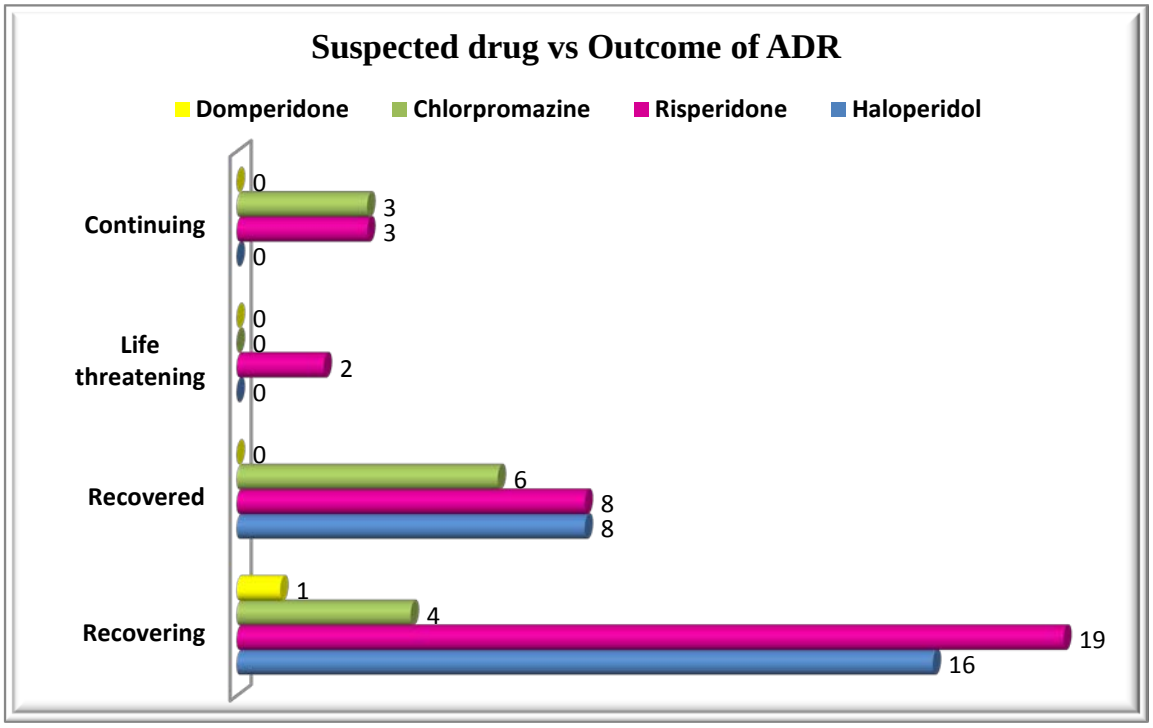
- The patients requiring initial hospitalization were almost equal in those using Haloperidol & Risperidone. Whereas prolonged hospitalization and intervention was highly required in those using Risperidone.

SUSPECTED DRUG VERSUS OUTCOME OF THE ADR

Table 25: Distribution of Suspected Drug versus Outcome of the ADR

Suspected drugs	Outcome of ADR				Total
	Recovering	Recovered	Life threatening	Continuing	
Haloperidol	16	8	0	0	24
Risperidone	19	8	2	3	32
Chlorpromazine	4	6	0	3	13
Domperidone	1	0	0	0	1

Figure 25: Distribution of Suspected Drug versus Outcome of the ADR



- Among the above suspected drugs, Risperidone produced a life threatening reaction. Recovery was almost similar with Risperidone , Haloperidol, & Chlorpromazine. Majority of the patients using all these

DISCUSSION

AGE

Table 1 and Figure 1 shows that 44% of DIP was common in the age group of 51- 60 years. 26% of DIP was common in the age group of 41–50 years followed by 12% in the age groups of 61-70 years and 21-30 years. About 6% of DIP was seen in the age group of 31- 40 years. Hence the most common age group affected was 51- 60 years. Bondon-Gitton E et al in their study found that DIP were mostly seen in the age group of 60-79 years.[35] R J Harde et al in their study found that Harde R J et al in their study found that the median age group who developed DIP was 61years.[36]

GENDER

Table 2 and Figure 2 shows that DIP was found to be more common in females (70%) compared to males (30%). Bondon-Gitton E et al in their study found that DIP was mostly seen in females (60%), which was almost similar to our study.[35] In an another study done by Harde R J et al, found that DIP was mostly seen in females (60%) in their study, which was almost similar to our study.[36]

PROFILE OF DRUG REACTION

Table 3A and Figure 3 had shown the various manifestation profile of DIP. Totally 13 types of manifestations occurred in the patients. Among these, bradykinesia was found to be the most common manifestation (82%), followed

by tremor (66%), rigidity (60%), and poverty of speech (50%). Less than 50% of patients developed gait disturbances (34%), Tardive dyskinesia (18%), Akathisia (16%). Less than 10% of patients developed Sialorrhea (8%), Sleepleesness and Perioral tremors (4%). 1% of patients developed Muscular dystonia, Neuroleptic malignant syndrome, and Oculogyric crisis.

Bondon-Gitton E et al in their study found that rigidity was the most common manifestation.[35] Harde R J et al; also found that in their study rigidity was the most common manifestation. [36] But in our study we found that bradykinesia was found to be the most common manifestation.

Table 3B showed different combinations of manifestations of DIP. More than one symptom occurs in the same patient. 10% of the patients developed the classical triad of DIP, bradykinesia, rigidity, and tremor.16% people developed a combination of tremors, rigidity, bradykinesia, and poverty of speech, which is the most common combination of symptom. Jimenz- Jimenz F J et al in their study has stated that it is possible for a single drug to cause 2 or more types of extrapyramidal symptoms in the same patient, [37] which was proved to be similar in our study also where the same patient has developed two or EPS.

SUSPECTED DRUGS

Table 4A, 4B and Figure 4A, 4B show the frequency of various drugs involved in causing DIP. These drugs fall under the group of dopamine antagonists like antipsychotics, and prokinetics. Atypical antipsychotic drug,

risperidone (64%) was the most common suspected drug causing DIP. Of the typical antipsychotic drugs, Haloperidol (48%), and Chlorpromazine (26%) were found as suspected drug to cause DIP. Of the prokinetics, domperidone (2%) was found as suspected drug to cause DIP.

So in our study, the most common causative drug group to cause DIP belongs to antipsychotic drugs, in which atypical antipsychotic drug risperidone was found to cause more DIP than typical antipsychotics. This was because most of the patients were treated with risperidone when compared to other drugs. The usage of typical antipsychotics was not so common when compared to atypical antipsychotics for treating various psychiatric diseases. Most of the psychiatrist prefers to use atypical antipsychotics as they found to cause less extrapyramidal symptoms with good efficacy when compared to typical antipsychotics.

Eventhough risperidone was an atypical antipsychotic drug, it has more affinity towards D_2 receptor and hence it causes more extrapyramidal symptoms when compared to other atypical antipsychotics. This indicates that risperidone have brought only relative avoidance of EPS, which urges for the search for novel antipsychotic drug without EPS. Weiden P J, in his study has stated that EPS remains as a significant problem even in the era of second generation (SGAs) or atypical antipsychotics. He states that most of the novel atypical antipsychotics can still cause EPS, and when it occurs they tend to be less severe when compared to typical antipsychotics. He also states that reduced EPS was not the same as no EPS. He states that EPS incidence differs

among the newer SGAs, with risperidone ranking as the most common causative agent, and clozapine and quietiapine with least propensity to cause EPS. [38]

Domperidone being a D_2 receptor antagonist has found to cause DIP in this study. K.D. Tripathi states the reason behind this as follows; it is chemically related to haloperidol but pharmacologically related to metoclopramide. It is used as antiemetic and prokinetic drug, attributed to D_2 receptor blockade in upper gastro intestinal tract. It crosses blood brain barrier poorly, hence extrapyramidal side effects are rare.[1] Bolegha et al in his review states that domperidone has safe neurological profile attributed to its poor penetration of blood brain barrier; yet, there were many reports on domperidone causing extrapyramidal side effects. This was explained by the presence of defective blood brain barrier in case of elderly, post brain surgery and cerebral infarction.[39]

Table 3B show that, even after development of EPS with a drug, two drugs with same potential to cause EPS were prescribed to the same patient. Bondon-Gitton E et al in their study found that antipsychotics were the most common group of drug to cause DIP.[35]

CONCOMITANT MEDICATIONS AND CO-MORBID CONDITIONS

All the patients were prescribed with one or more concomitant medications. These drugs were prescribed for the associated co-morbidities like

alcoholic dependence, depression, hypertension, T2DM, hypothyroidism, seizure disorder, GERD, monilial esophagitis, and mental retardation.

DIAGNOSIS

Table 6 and Figure 6 show that all these drugs were used to treat psychiatric diseases except domperidone which was used to treat GERD. Most common psychiatric disease for which the patients were taking antipsychotic drugs was schizophrenia (52%). 10% of patients suffered from BPAD, followed by acute psychosis and chronic depression (8%), behaviour disorder and depressive psychosis (6%), alcoholic psychosis (4%), GERD, OCD and psychosis (1%). Harde R J et al; found that in their study schizophrenia was the most common diagnosis for which the patients were taking antipsychotic drugs which exactly found to be similar in our study.[36]

DURATION OF UNDERLYING ILLNESS

Table **7** and figure 7 shows that duration of illness varies from less than 2 years to maximum of 10 years. Less than 2 years (42%) was found to be the most common duration of illness followed by 3-4 years (28%), 5-6years (9%), and 6-10 years (6%).

ONSET OF REACTION:

Table 8 and Figure 8 show that onset of reaction after drug introduction varies from 1 month to 6 years. Onset of reaction denotes the duration of exposure to suspected antipsychotic drugs. Most of the patient developed drug

reaction after 1to 2yrs of starting the treatment, followed by 1 month to below one year of duration. The maximum onset of reaction was found to be 6 years after starting of treatment.

Harde R J et al; found that in their study the duration of exposure varied widely from 4 weeks to 22yrs. The median duration of exposure was 3 years and the mean duration of exposure was 6.3years, [36] and this study co-relates similarly with our study in the minimal onset range and median and but differs in maximal onset range and mean.

SERIOUSNESS OF REACTION

Table 9 Figure 9 show the seriousness of the adverse drug reactions. Most of the patients required interventions (50%) like cessation of the suspected drug, treatment with one of the centrally acting anticholinergic drugs and change of drug to those having less potential to cause EPS. Rest of the patients required hospitalization initially (40%), or their hospitalization was prolonged (10%) due to EPS.

Table 17 and Figure 17 show that all the ADRs required various interventions in all age groups and no statistical difference was found in between age and seriousness of reaction. Table 19 and Figure 19 show that the distribution of seriousness of reaction was different among male and female patient. Female patients required more intervention and hospitalization than male patients. But there is no statistical significant difference found between

sex and seriousness of reaction when Chi-square test is applied as the P value is .168

OUTCOME

Table 10 and Figure 10 show the distribution of the outcome of the drug induced reaction. Most of the patients were in recovering state (62%). About 28% of patients recovered from their illness. Few of the patients had their reaction continuing (6%) and few had life threatening reactions (4%). Bondon-Gitton E et al in their study found that about 88.7% patients were improving from their illness, showing good favourable outcome when compared to our study where 62% were improving.[35] Harde R J et al; found that in their study 8% of people got completely recovered from the reaction, which is very low when compared to our study which had complete recovery in 28% of patients.[36]

Table 18 and Figure 18 show that Most of the patients in all age groups were in recovery phase especially more common in the age group ranging from 51-60 yrs. Very few patients recovered. There is no significance between age groups and outcome as the P value = .548

CAUSALITY ASSESSMENT- WHO SCALE and NARANJO SCALE

Table 11 & 12; Figure 11 & 12 show the causality assessment of the drug induced reaction. When the above two scales were used to assess the causality, they both had shown same results as follows. Maximum ADRs were categorized as probable (88%) and rest of them were of possible category (12%). Mandal et al in their study used Naranjo's scale for causality

assessment and found that most of the ADRs were of “probable” and “possible” category, which was found to be similar to our study.[40]

ADR SEVERITY ASSESSMENT SCALE

Table 13 and Figure 13 show that all the ADRs (100%) were of moderately severe requiring dose reduction or discontinuation of the suspected drug and change to another drug. Bondon Guitton et al in their study states that 43.9% of cases found to be of “serious” category among 155 cases of DIP [41], which varied widely when compared to our study which consists of 100% of moderate severity.

PREVENTABILITY ASSESSMENT SCALE

Table 14 and Figure 14 show that 60 % of ADRs were probably preventable & 40 % were not preventable. All the drugs were indicated for their psychiatric illness, but sometimes when the patient develops DIP for one antipsychotic drug, after discontinuing it they were given another antipsychotic drug of the same group or different group which also has the high propensity to cause EPS. This overlapping of drugs with same potency to cause DIP could have been avoided to prevent the development of DIP.

PROPHYLAXIS AND TREATMENT WITH THP

Table 15 and Figure 15 show that about 60% of the patients were prophylactically treated with THP. Harde R J et al, states that anticholinergics were traditionally used either as prophylaxis or as treatment against DIP. [36]

Table 16 and Figure 16 show that the entire patient who developed DIP was treated with THP, and all of them showed improvement after treatment. Mamo, D.C.,et al states that in younger patients anticholinergic agents remain the mainstay pharmacological management of DIP caused by antipsychotics.in elderly patients, amantadine was better tolerated with efficacy similar to anticholinergic agents. And also they state that routine use of the prophylactic anticholinergics was not needed and was clearly contraindicated in the elderly patients.

Limitations of the Study: The study was done in small group of 50 patients. It was done only in the departments of Psychiatry and Neurology; if this study was extended to other departments then other suspected drugs causing DIP would have been identified. Therapeutic drug monitoring was not done which may be helpful to avoid the toxic dose concentration. In this study rechallenge for drug induced reaction with suspected drug was not performed due to ethical consideration.

CONCLUSION

The study was undergone to analyze the profile of drug induced Parkinsonism, and to assess the causality, severity and preventability in the outpatient department of Psychiatry and Neurology. Total patients enrolled with DIP during one year study duration were 50. The aim and objectives of the study were met. Most common age group affected with DIP is 51-60 yrs. DIP was found to be more common in females when compared to males. Antipsychotics were the most common group of drug suspected to cause DIP. Domperidone was found to cause DIP, which was found in one patient.

Bradykinesia was considered as most common symptom of DIP, followed by tremor and rigidity. Risperidone, the atypical antipsychotic was most commonly used and was highly found to cause DIP. All the patients were using one or more than one concomitant medications. Most common diagnosis was schizophrenia followed by bipolar affective disorder. Most of the patient developed drug reaction after 1to 2yrs of starting the treatment.

Maximum ADRs were probable (88%) and rest of them were possible (12%). All the ADRs were moderately severe requiring dose reduction or discontinuation of the suspected drug and change to another drug. 60 % of ADRs were probably preventable & 40 % were not preventable. All the patients with ADRs showed improvement after treatment with THP.

Thus this study gives overall view about drug induced Parkinsonism among the attended the outpatient department of Psychiatry and Neurology in a

tertiary care hospital. And this study shows that drugs were important etiological factor for DIP and clinicians should be vigilant about the safety profile monitoring of the medications prescribed. Hence Pharmacovigilance programmes to be implemented efficiently and continuous vigilance is needed to detect ADRs thereby making drug therapy safe and effective.

IMPACT ON THE PATIENT

DIP can cause considerable physical disability, subjective discomfort and distress to the patients. It was stated as the most common reason for the poor compliance with the medications. It unnecessarily increases the cost of treatment which adds to financial burden of the patient. It can confuse the clinical assessment of the exact medical condition of the patient as the symptom overlaps with that of the psychiatric illness. Hence DIP was harmful and serves no beneficial purpose to the patient.

PREVENTIVE APPROACH

- Prevention is always better than cure. Since the treatment of drug induced movement disorders remains challenging, a preventive approach is always better and preferable.
- The use of the suspected and offending drugs should be strictly restricted to appropriate indications and should be definitely avoided when a better drug is available for the same.
- Early process to avoid DIP is to keep a high index of suspicion for all the possible causes, by maintaining a thorough list of the drugs

prescribed to the patient and also search for other possible sources of getting the offending drugs.

- Prescribers should be vigilant for DIP, especially in elderly, in those patients taking multiple drug therapy, in those who have previous history of EPS, in those on prolonged treatment profile, familial history, and in those with genetic variants to develop idiopathic Parkinson's disease.
- **"ADR alert card"** can be issued to the patients who had developed DIP, stating the type of ADR and the suspected drug causing the ADR. This will help in future to identify the patients vulnerable to develop ADR and helps to avoid prescribing the offending drug in such patients.

FUTURE SCOPE

- Better characterisation of the neurochemical profile of the affected system and its function should be focused to have better treatment.
- Novel drugs with high selectivity, good efficacy and less side effect profile should be developed to ensure good patient compliance.
- Further pharmacovigilance studies on DIP for long duration should be conducted to widen the knowledge about the existing trends, changing trends and overall profile of DIP.

BIBLIOGRAPHY

1. Tripathi K D. Essentials of Medical Pharmacology. 7thed. New Delhi: Jaypee brothers, 2013, 1:2; 664-667.
2. Sharma H L, Sharma K K: Principles of Pharmacology: 2nd edition; Paras medical publisher, Hyderabad, 2011; 69.
3. Sethi K D. Movement disorders induced by dopamine blocking agents. Semin Neurol. 2001; 21:59–68.
4. Esper CD, Factor SA. Failure of recognition of drug-induced Parkinsonism in the elderly. Mov Disord.2008; 23:401–404.
5. Commission on Anesthetics. Lancet, 1893; i: 629-38.
6. Dyke SC. Agranulocytosis and amidopyrine . British Medical Journal. 1936; 2(3957):911-914.
7. The 1937 Elixir Sulfanilamide Incident.
8. Randell T. Thalidomide's back in the news, but in more favorable circumstances .JAMA, 1990; 263:467-68.
9. PAHUJA, Ritu et al. Awareness on Adverse Drug Reaction Reporting System in India: A Consumer Survey. American Journal of Phytomedicine and Clinical Therapeutics, [S.l.], v. 2, n. 12, p. 1361-1369, Dec. 2014. ISSN 2321-2748.
10. Kaplan & Sadock's: Comprehensive textbook of psychiatry, vol: 2,9th ed, 31:2996

11. Tripathi K D. Essentials of Medical Pharmacology. 7th ed. New Delhi: Jaypee brothers, 2013, 1:2
12. Sharma H L, Sharma K K: Principles of pharmacology: 2nd edn; Paras medical Publisher, Hyderabad, 2011; 69.
13. Stephen M D B, Talbot J C C and Roultedge PA, the detection of new adverse drug reactions. Basingstoke, Macmillan Publishers ltd, UK, Ed.(1998), 546pp.
14. Laurence D R, Bennet P N and Brown M J. Clinical Pharmacology. Edinburgh: Churchill and Livingstone Co, 1997, 710pp.
15. http://www.WHO-umc.org
16. Philip J Gregory, Karen L Keir. Medication Misadventures: Adverse drug reaction Information: A guide for Pharmacists' ed. Patrick Malone, McGraw Hill Professional, 2000:487-518.
17. Post Approval Safety Data management: Definitions and standards for expedited reporting.ICH E2D.Current step 4 - version dated November 2003.
18. Levine RR Factors modifying the effects of drugs in individuals. In: Pharmacology: drug actions and reactions. Boston (MA): Little Brown and Co.1973:261-9.
19. Stephen M D B, Talbot J C C and Routledge P A, The detection of new adverse drug reactions. Basinstoke, Macmillan Publishers Ltd, UK, Ed. (1998), 546pp.

20. Hunziker, et al. 1997 “Comprehensive hospital drug monitoring (CHDM): adverse skin reactions 20 year survey.” Allergy, 52:388-393.
21. Pharmacovigilance: Ensuring the Safe Use of Medicines - WHO Policy Perspectives on Medicines, No. 009, October 2004;1-6pp
22. ICH Guidance E2D; Post approval Safety Data Management: Definitions and standards for expedited reporting. November 2003.
23. Thakrar BT, Grundschober SB, Dossegger L. Detecting signals of drug –drug interactions in a spontaneous reports database.Br J Cin Pharmacology 2007;64(4):489-95.
24. www.cdsco.nic.in/pharmacovigilance_intro.htm
25. Goodman & Gilman’s The Pharmacological Basis of Therapeutics -12th edition, Mc Graw Hill, 2011, 16: 351- 359; 417-451.
26. P.R. Burkhard / Parkinsonism and Related Disorders. 20S1 (2014); S108-S112.
27. Kaplan & Sadock’s: Comprehensive textbook of psychiatry, volume:2,9th edition, 31:2997
28. Diagnostic and statistical manual of mental disorders. 4th ed. Text rev. Washington, DC: American psychiatric association; 2000.
29. Janicak PG, Davis JM, Preskorn SH, Ayd FJ Jr, Marder S: Principles of Psychopharmacotherapy. 4th ed. Philadelphia: Lippincott Williams & Wilkins; 2006.
30. Hae-Won Shin, Sun Ju Chung: Drug Induced Parkinsonism. Review. J Clin Neurol 2012;8:15-21

31. Maria Victoria G, Alvarenz, Virgilio Gerald H, Evidente. Understanding drug induced Parkinsonism: separating pearls from oysters. Neurology. 2008; 70(8):e32-e34

32. Naranjo CA, Busto U, Sellers EM, Sandor P, Ruiz I, Roberts EA, et al. A method for estimating the probability of adverse drug reactions. Clin Pharmacol Ther.1981; 30:239-45.

33. Hartwig SC, Siegel J, Schneider PJ. Preventability and severity assessment in reporting adverse drug reactions. Am j Hosp Pharm. 1992;49:2229-32

34. Schumok GT, Thorton JP. Focusing on the preventability of adverse drug reactions. Hosp Pharm. 1992; 27:538

35. Bondon-Guitton, E., Perez-Lloret, S., Bagheri, H., Brefel, C., Rascol, O. and Montastruc, J.-L. (2011), Drug-induced Parkinsonism: A review of 17 years' experience in a regional pharmacovigilance center in France. Mov. Disord., 26: 2226–2231. doi:10.1002/mds.23828

36. Harde R J, Lees A J, Neuroleptic-induced Parkinson's syndrome: clinical features and results of treatment with levodopa. Journal of Neurology, Neurosurgery, and Psyhiatry 1988 Jun;51(6):850-4

37. Jimenz- Jimenz F J, Garcia- Ruiz P J,Molina J A. Drug induced movement disorders: Drug Saf. 1997 Mar; 16(3):180-204.

38. Weiden P J. EPS profiles: The antipsychotics are not all the same. J Psychiatr Pract. 2007 Jan; 1391): 13-24.

39. Saeed A. Bohlega, Nurah B. Al-Foghom. Drug induced Parkinson’s disease. A clinical review: Neurosciences 2013 Jul;18(3):215-21

40. Ananya Mandal, suparna chatterjee, Shyamal Kumar Das, Amar Mishra. Drug safety monitoring in patients of movement disorders of a tertiary care hospital: Indian J Pharmacol Aug 2010; 42(4):249-251.

41. Bondon-Guitton, E., Perez-Lloret, S., Bagheri, H., Brefel, C., Rascol, O. and Montastruc, J.-L. (2011), Drug-induced Parkinsonism: A review of 17 years' experience in a regional pharmacovigilance center in France. Mov. Disord., 26: 2226–2231. doi:10.1002/mds.23828

42. Mamo, D.C., Sweet, R.A. & Keshavan, M.S. Managing antipsychotic-induced Parkinsonism. Drug-Safety (1999) 20: 269. doi:10.2165/00002018-199920030-00006

ANNEXURE: I

WHO CAUSALITY CLASSIFICATION[15]

CAUSALITY	ASSESSMENT
Certain	• Event or laboratory test abnormality, with plausible time relationship to drug intake • Cannot be explained by disease or other drugs • Response to withdrawal plausible(pharmacologically, pathologically) • Event definitive pharmacologically or phenomenological(i.e. an objective and specific medical disorder or a recognized pharmacological phenomenon) • Rechallenge satisfactory, if necessary
Probable/Likely	• Event or laboratory test abnormality, with reasonable time relationship to drug intake • Unlikely to be attributed to disease or other drugs • Response to withdrawal clinically reasonable • Rechallenge not required
Possible	• Event or laboratory test abnormality ,with reasonable time relationship to drug intake • Could not be explained by the disease or other drugs • Information on drug withdrawal may be lacking or unclear
Unlikely	• Event or Laboratory test abnormality with a time to drug intake that makes a relationship improbable(but not impossible) • Disease or other drugs provide plausible explanations
Conditional/ Unclassified	• Event or Laboratory abnormality • More data for proper assessment needed, or • Additional data under examination
Unassessable / Unclassifiable	• Report suggesting an adverse reaction • Cannot be judged because information is insufficient or contradictory • Data cannot be supplemented or verified

ANNEXURE: II

NARANJO ALGORITHM

To assess causality of adverse drug reaction, answer the following questionnaire and score it

S.no	Questions	Yes	No	Do not know	Score
1	Are there previous conclusive reports on this reaction?	+1	0	0	
2	Did the adverse event occur after the suspected drug was administered?	+2	-1	0	
3	Did the adverse reaction improve when the drug was discontinued or a specific antagonist was administered?	+1	0	0	
4	Did the adverse reaction reappear when the drug was re-administered?	+2	-1	0	
5	Are there alternative causes (other than the drug) that could have on their own caused the reaction?	-1	+2	0	
6	Did the reaction reappear when the placebo was given?	-1	+1	0	
7	Was the drug detected in the blood (or other fluids) in concentrations known to be toxic?	+1	0	0	
8	Was the reaction more severe when the dose was increased or less severe when the dose was decreased?	+1	0	0	

9	Did the patient have a similar reaction to the same or similar drugs in any previous exposure?	+1	0	0	
10	Was the adverse event confirmed by any objective evidence?	+1	0	0	
	Total				

Category	**Score**
Definite	≥9
Probable	5-8
Possible	1-4
Doubtful	0

ANNEXURE: III

MODIFIED SCHUMOK AND THORTON SCALE –

PREVENTABILITY ASSSESSMENT SCALE

Definitely preventable

1. Was there a history of allergy or previous reactions to the drug?
2. Was the drug involved inappropriate for the patient's clinical condition?
3. Was the dose, route or frequency of administration inappropriate for the patient's age, weight or disease state?
4. Was a toxic serum drug concentration (or laboratory monitoring test) documented?
5. Was there a known treatment for the adverse drug reaction?

Probably preventable

6. Was required therapeutic drug monitoring or other necessary laboratory tests not performed?
7. Was a drug interaction involved in the ADR?
8. Was poor compliance involved in ADR?
9. Were preventive measures not prescribed or administered to the patient?

Not preventable

If all above criteria not fulfilled

ANNEXURE: IV

MODIFIED HARTWIG AND SIEGEL SCALE -

ADR SEVERITY ASSESSMENT SCALE

Mild **Level 1:** The ADR requires no change in treatment with the suspected drug (or) **Level 2:** The ADR requires that the suspected drug be withheld, discontinued or otherwise changed, and there is no increase in the length of the stay
Moderate **Level 3**: The ADR requires that the suspected drug be withheld, discontinued or otherwise changed, and / or an antidote or other treatment is required. There is no increase in the length of the stay (or) **Level 4 (a):** Any level 3 ADR that increase the length of the stay by at least one day (or) **Level 4 (b):** The ADR is the reason for the admission
Severe **Level 5:** Any level 4 ADR that requires intensive medical care (or) **Level 6:** The ADR causes permanent harm to the patient (or) **Level 7:** The ADR either directly or indirectly leads to the death of the patient

ANNEXURE: V

PROFORMA

REF. NO:

DATE:

NAME:
AGE/SEX:

ADRESS/PHONE NUMBER:

HISTORY:

DRUG H/O:

Medication details:

Name of the medication	Dose , dosing schedule	Route of administration	Duration of prescription	ADRs	Outcome

SUMMARY OF ILLNESS:

Duration	Severity	Impact of disease	Reason for change of drug, if any	Impact of treatment

DIAGNOSIS:

INVESTIGATIONS:

TREATMENT:

ANNEXURE: VI

CONSENT FORM

Title: 'Drug Induced Parkinsonism – A Causality, Severity, & Preventability Assessment Study In A Tertiary Care Hospital '

Study Centre: Govt. Kilpauk Medical College, Chennai-10

Patient's Name: O.P. No.:

Patient's Age/sex:

I confirm that I have understood the purpose and procedure of the above study. I had the opportunity to ask questions and all my doubts have been answered satisfactorily.

I understand that my participation in the study is voluntary and that I am free to withdraw at any time without my legal rights being affected.

I understand that the members of the ethics committee and the investigators involved in the study will not need my permission to look at my health records, both in respect to the current study and any other further research that may be conducted in relation to it. However, I understand that my identity will not be revealed in any information released to third parties or published, unless as required under the law. I agree not to restrict the use of any data or results that may arise from this study.

I hereby consent to participate in this study.

Patient's Signature/ Thumb Impression:

Patient's Name and address:

Witness Signature/ Thumb Impression:

Witness Name and address:

Investigator's Signature:

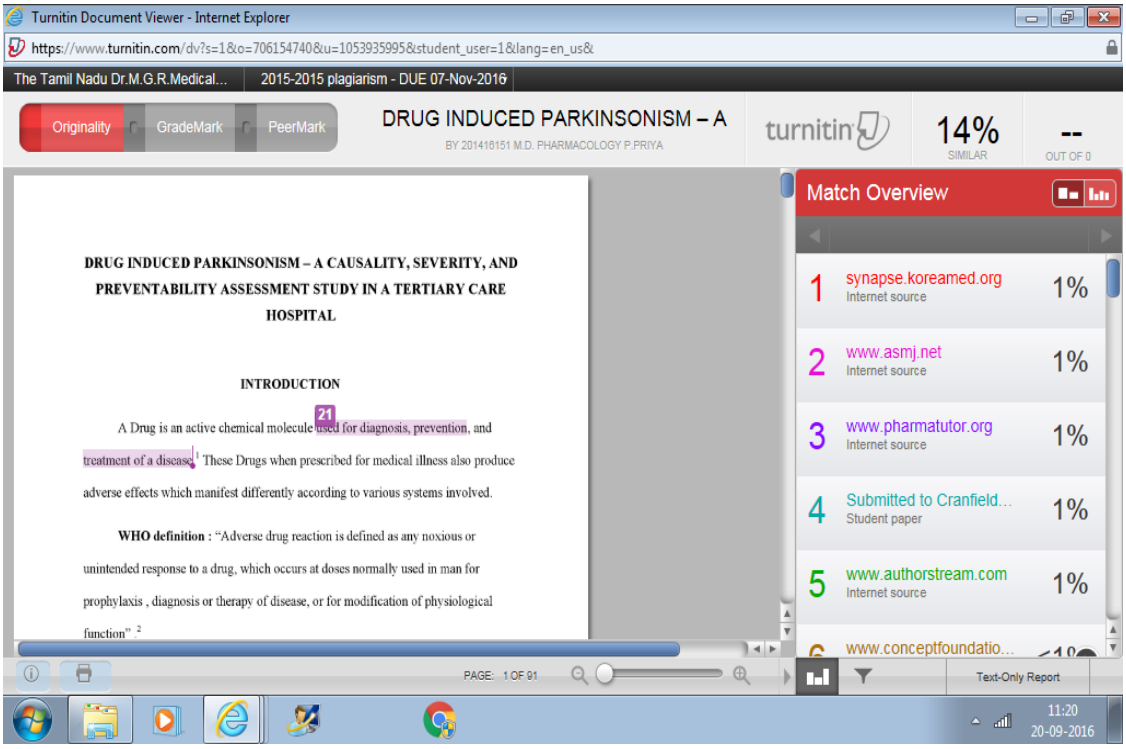
Name of the Investigator:

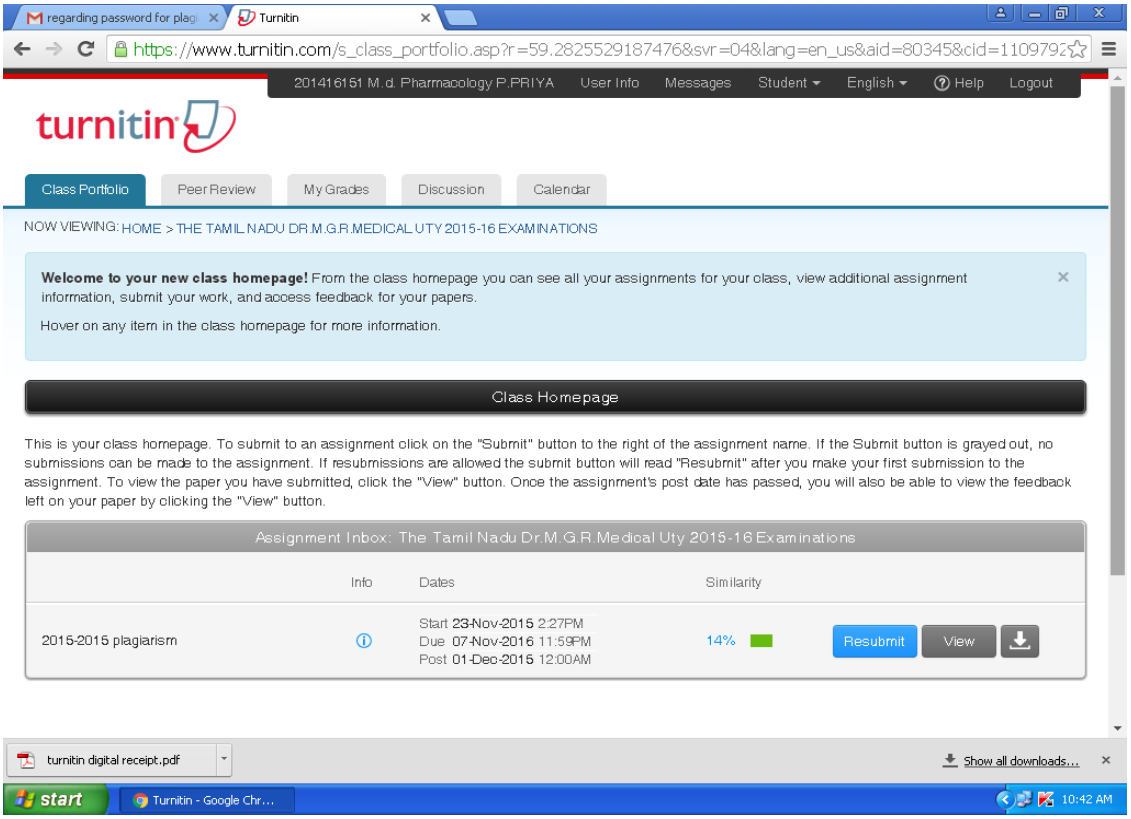
Date:

Place:

ANNEXURE: XII

TURNITIN DIGITAL RECEIPT





ANNEXURE- XI

MATER SHEET

No	Age (yrs)	Gender	Profile of adverse drug reaction (DIP)	Suspected drugs	concomitant medications	Diagnosis	Duration of illness (yrs)	Onset of reaction after Treatment (yrs)	Seriousness of reaction
1	62	F	T, GD, PS	R	Y	1	3	0.6	1
2	62	F	B, R	R	Y	6	9	6	3
3	60	M	T, B, PT,TD	R , CPZ	Y	1	3	1	2
4	59	F	T, GD, PS	D	Y	7	2	0.6	3
5	58	F	T, B, R	CPZ, HLP	Y	2	6	5	3
6	58	F	B, R	CPZ, HLP	Y	2	6	5	3
7	53	M	B, T,PS , SL, S	HLP , CPZ	Y	10	5	4	1
8	53	F	T, B, R, PS	HLP , R	Y	2	2	1	3
9	53	F	T, B, R, PS	R	Y	2	1	0.9	3
10	53	M	B, T,PS , SL, S	HLP , CPZ	Y	10	5	4	1
11	50	F	T, B, R	R	Y	2	3	2	3
12	50	F	T, GD, PS	R	Y	4	1	0.2	3
13	50	F	B, R	R	Y	2	3	2	3
14	48	M	T, GD, PS ,TD	HLP	Y	3	4	11	1
15	48	F	GD, PS , TD	HLP	Y	3	4	1	1
16	48	M	T, GD, PS ,TD	HLP	Y	3	4	1	1
17	46	F	T, B, R , PS,PT	R	Y	2	1	0.1	1
18	45	M	T,B, GD, PS	R	Y	6	5	4	1
19	45	F	T, B, R	R, CPZ, HLP	Y	4	1	0.2	3
20	42	F	T,B, GD, PS	R, CPZ, HLP	Y	2	3	2	3
21	42	F	B, R , MD	CPZ, HLP	Y	2	5	1	1
22	37	M	B, R	R	Y	4	1	0.2	3
23	65	F	T,B, GD, PS ,S, TD	HLP , R	Y	5	7	3	1
24	35	F	B, R, A	R	Y	5	7	6	1
25	60	M	T,B, GD, PS	R	Y	8	1	0.8	1
26	55	F	T, B, R	HLP	Y	2	2	1	3
27	57	M	T,B, GD, PS ,S, TD	HLP , R	Y	5	7	3	1
28	55	F	B, R, A	R	Y	5	7	6	1

29	31	F	T, GD, PS ,TD	R , CPZ	Y	1	2	2	2
30	61	M	B, R,OC	R	Y	2	2	3	1
31	53	F	T, GD, PS ,TD	R , CPZ	Y	1	2	2	2
32	60	F	B, Rj	HLP	Y	2	1	0.3	1
33	30	F	B, Rj	HLP	Y	2	1	0.3	1
34	29	F	B, R, A, NMS	R	Y	2	6	2	2
35	28	F	B, R, A	R	Y	9	3	2	`
36	47	F	T, B, R, PS	HLP	Y	2	2	1	1
37	27	M	T, B, R, PS	HLP	Y	2	2	1	1
38	52	M	T,B, GD, PS , TD	R	Y	2	3	2	3
39	24	F	T, B, R, PS	R	Y	2	1	0.2	1
40	22	M	T,B, GD, PS	R, CPZ, HLP	Y	2	4	3	3
41	55	F	T, B, R, PS	HLP , R	Y	2	1	0.3	3
42	50	F	B, R, A	HLP	Y	2	2	1	3
43	60	F	T, B, R, PS	R	Y	2	3	2	3
44	52	F	T, GD, PS	R	Y	2	1	0.2	3
45	57	F	B, R, A	HLP	Y	4	2	1	3
46	65	M	B, R, A	HLP	Y	2	4	3	3
47	62	F	T, B, R	R	Y	6	6	3	3
48	56	F	T, B, R, PS	CPZ, HLP	Y	2	4	2	3
49	51	M	T,B, GD, PS	R, CPZ, HLP	Y	2	6	3	3
50	54	F	B, R, A	R	Y	4	7	4	3

No	WHO scale	Naranjo scale	ADR severity assessment scale	Preventability assessment	Improvement after treatment	Prophylactic THP	Outcome	Lab investigations
1	2	2	2	3	Y	N	1	N
2	2	2	2	3	Y	N	2	N
3	2	2	2	3	Y	Y	4	N
4	2	2	2	3	Y	N	1	N
5	2	2	2	2	Y	Y	2	N
6	2	2	2	2	Y	Y	2	N
7	3	3	2	2	Y	Y	1	N
8	2	2	2	2	Y	N	1	N
9	2	2	2	3	Y	N	1	N
10	3	3	2	2	Y	Y	1	N
11	2	2	2	3	Y	Y	1	N
12	3	3	2	3	Y	Y	2	N
13	2	2	2	3	Y	Y	2	N
14	2	2	2	2	Y	N	1	N
15	2	2	2	2	Y	N	1	N
16	2	2	2	2	Y	N	1	N
17	2	2	2	3	Y	Y	1	N
18	2	2	2	3	Y	N	3	Focal demyelination (Drug induced)
19	2	2	2	2	Y	Y	2	N
20	2	2	2	2	Y	Y	1	N
21	2	2	2	2	Y	Y	2	N
22	2	2	2	3	Y	Y	2	N
23	2	2	2	2	Y	N	1	N
24	2	2	2	2	Y	N	1	N
25	2	2	2	2	Y	N	1	N
26	2	2	2	2	Y	Y	2	N
27	2	2	2	2	Y	N	1	N
28	2	2	2	2	Y	N	1	N
29	3	3	2	2	Y	N	4	N
30	2	2	2	3	Y	Y	1	N
31	3	3	2	2	Y	N	4	N
32	2	2	2	2	Y	Y	2	N
33	2	2	2	2	Y	Y	2	N
34	2	2	2	3	Y	Y	3	N
35	2	2	2	3	Y	N	1	N
36	2	2	2	2	Y	Y	1	N
37	2	2	2	2	Y	Y	1	N
38	2	2	2	3	Y	N	1	N

39	2	2	2	2	Y	Y	1	N
40	2	2	2	2	Y	Y	2	N
41	2	2	2	2	Y	N	1	N
42	2	2	2	2	Y	Y	1	N
43	2	2	2	3	Y	Y	1	N
44	3	3	2	3	Y	Y	1	N
45	2	2	2	3	Y	Y	1	N
46	2	2	2	2	Y	Y	1	N
47	2	2	2	3	Y	N	2	N
48	2	2	2	2	Y	Y	1	N
49	2	2	2	2	Y	Y	2	N
50	2	2	2	3	Y	Y	1	N

Figure (A): Communication channels in PvPI [24]

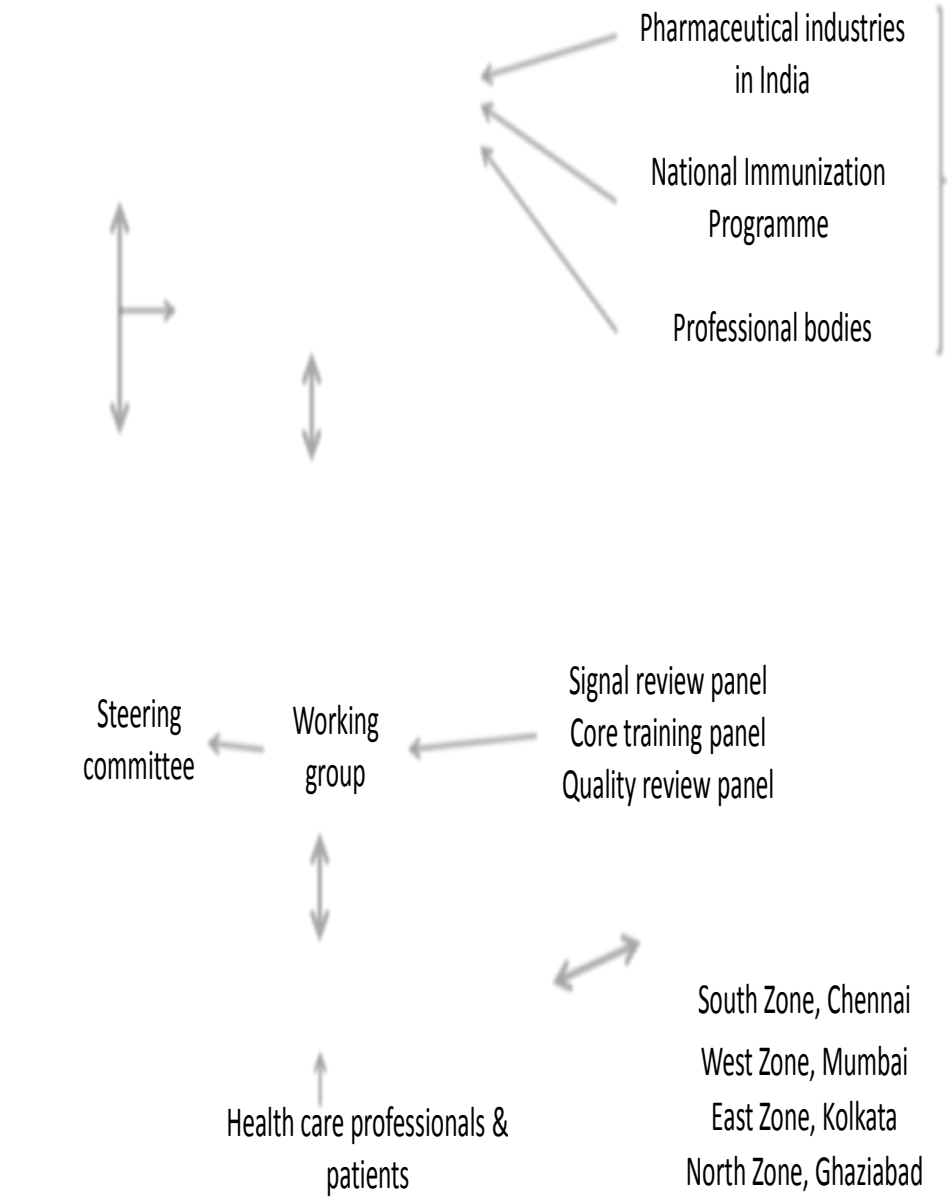


Figure (B): Synthesis of Dopamine

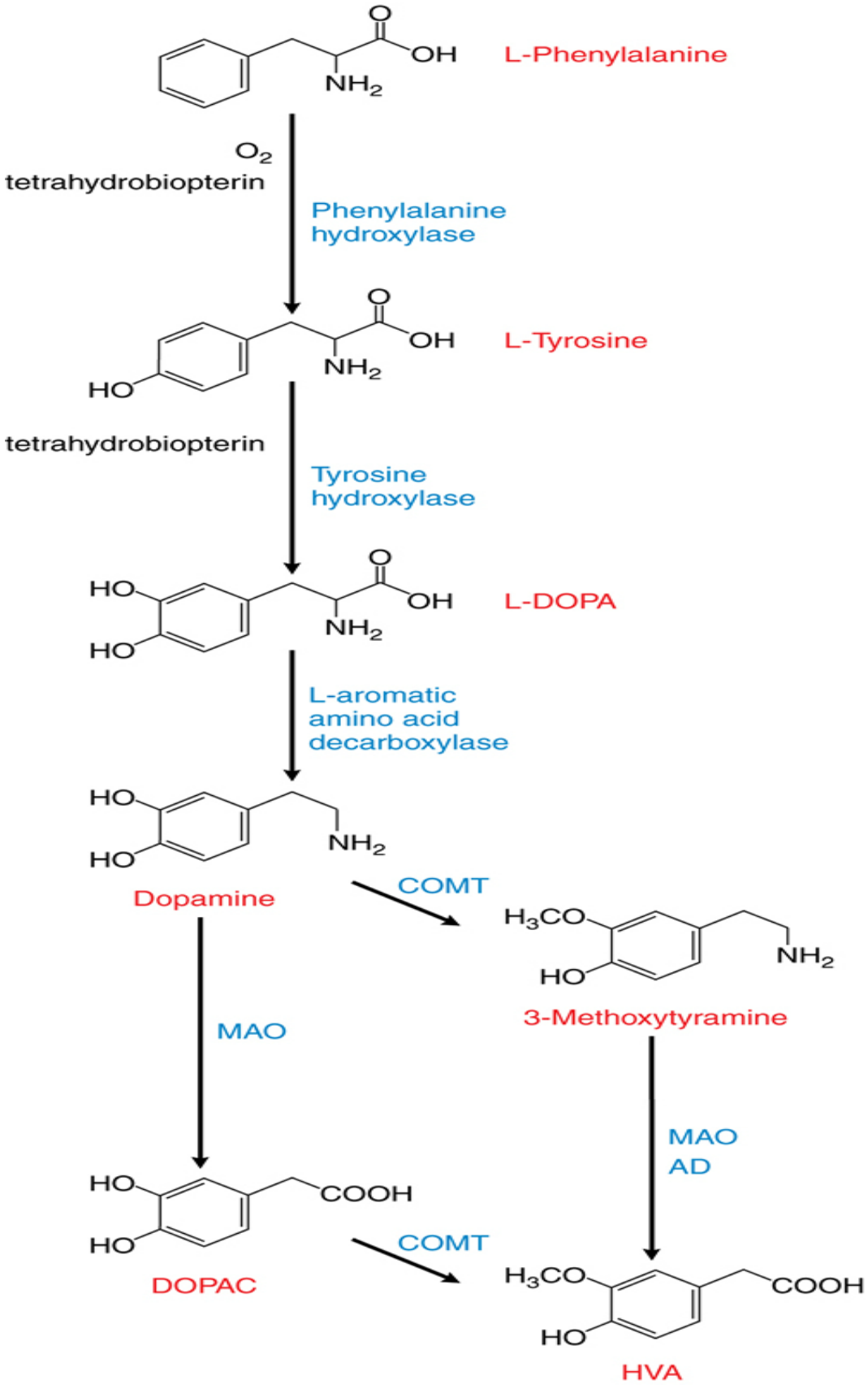


Figure (C): Storage, Release, and Metabolism of Dopamine

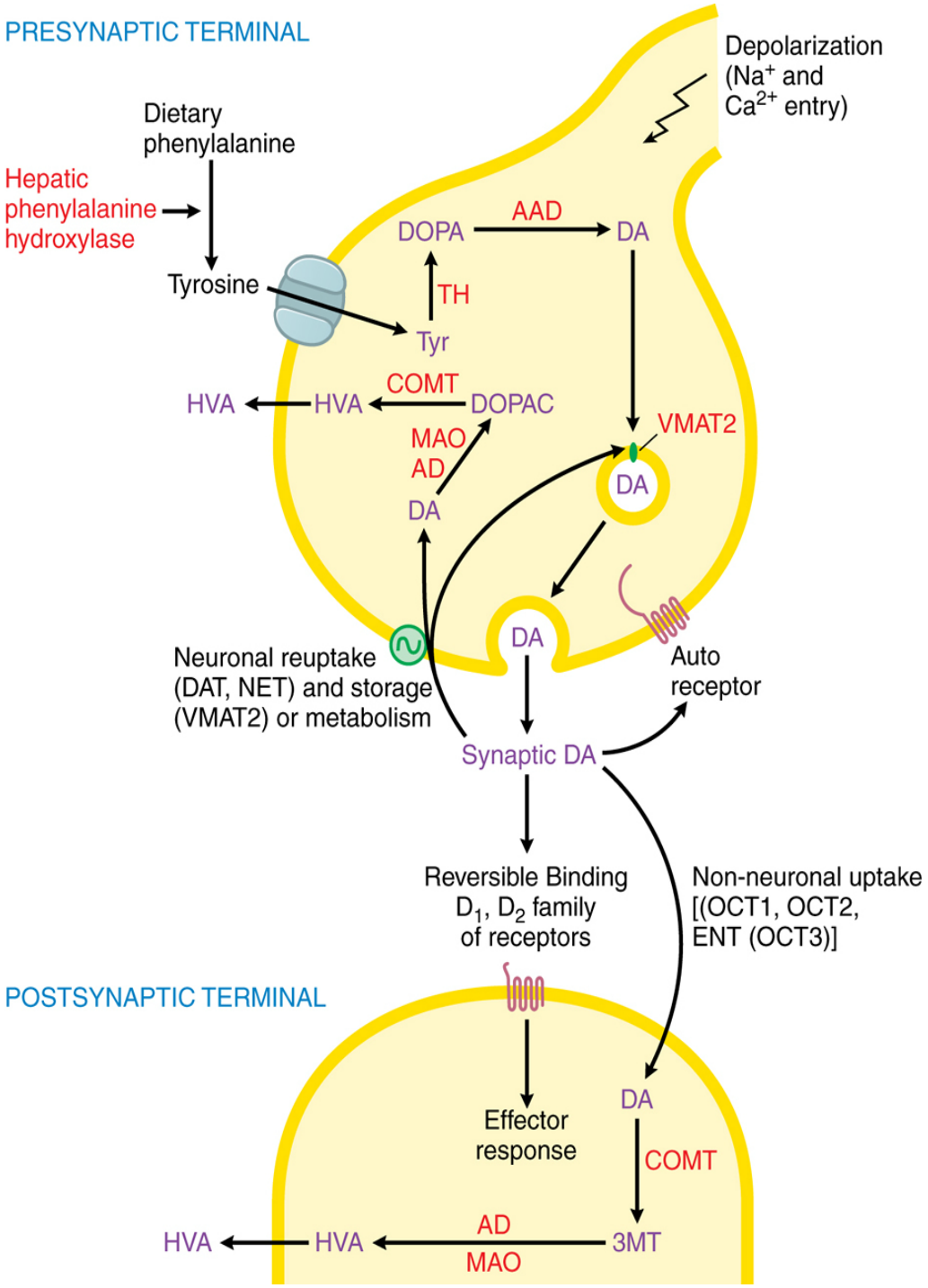
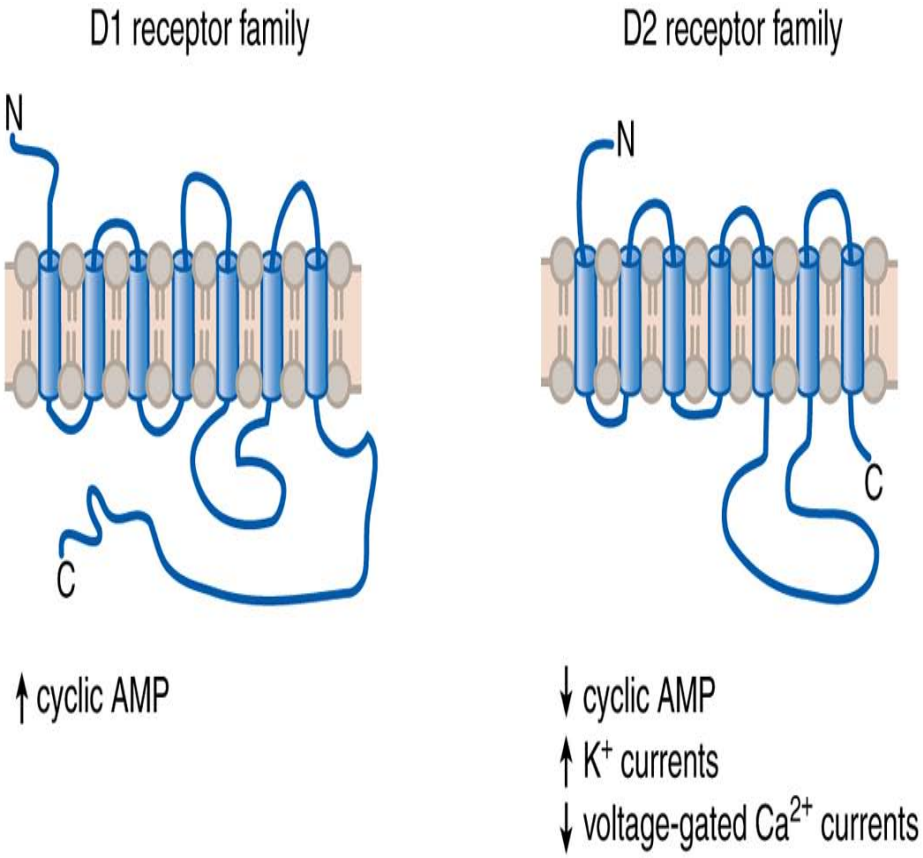


Figure (D): Dopamine Receptor Family and Distribution



D_1	D_5
• SNpr	• hypothalamus
• frontal cortex	• striatum
• nucleus Acc	• NAc
• hypothalamus	

D_2	D_3	D_4
•striatum	•n. accumbens	• PFC
•SNpc	•SNpc	• hypothalamus
•pituitary	•VTA	• amygdala
•PFC		• hippocampus

Figure (E): Anatomy of Dopamine Pathway Areas

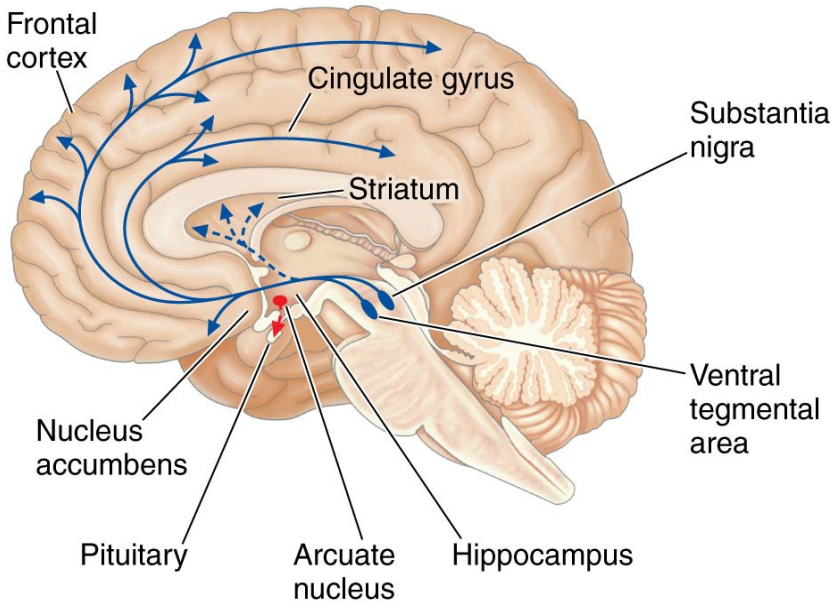


Figure (F): Dopamine pathways

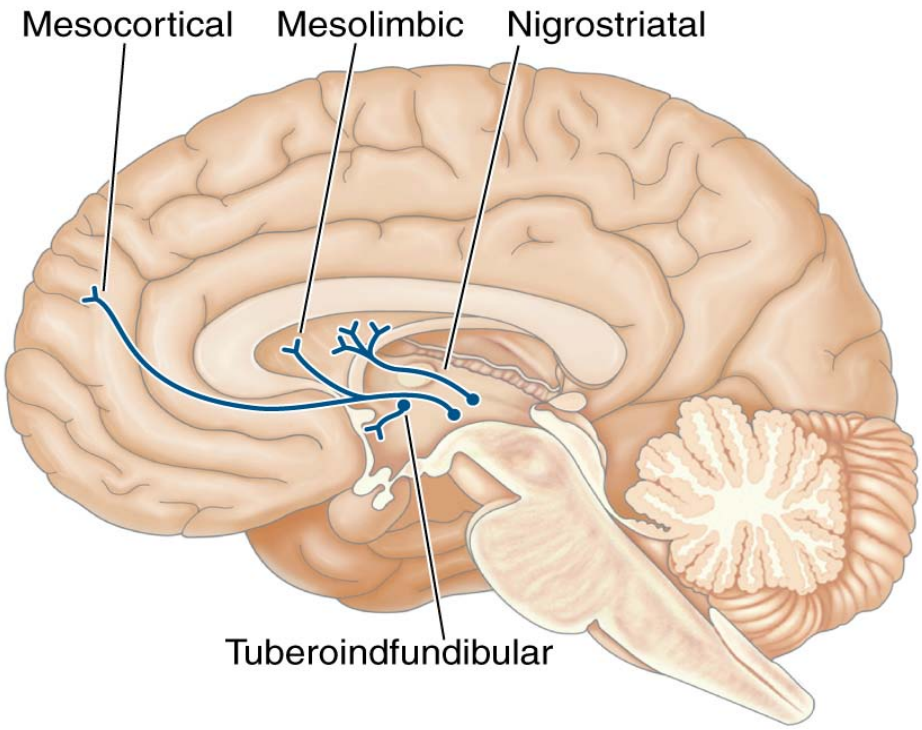


Figure (G): Mechanism of action of Antipsychotics

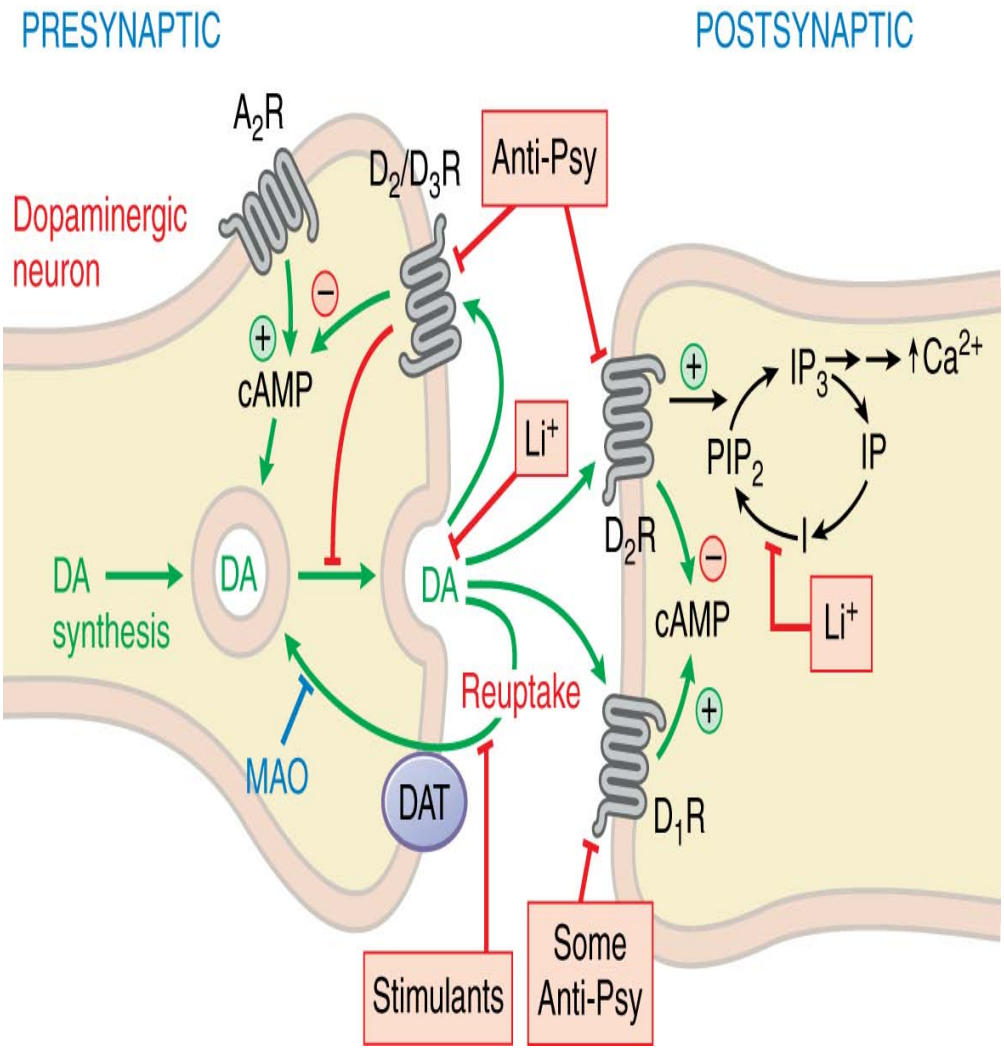
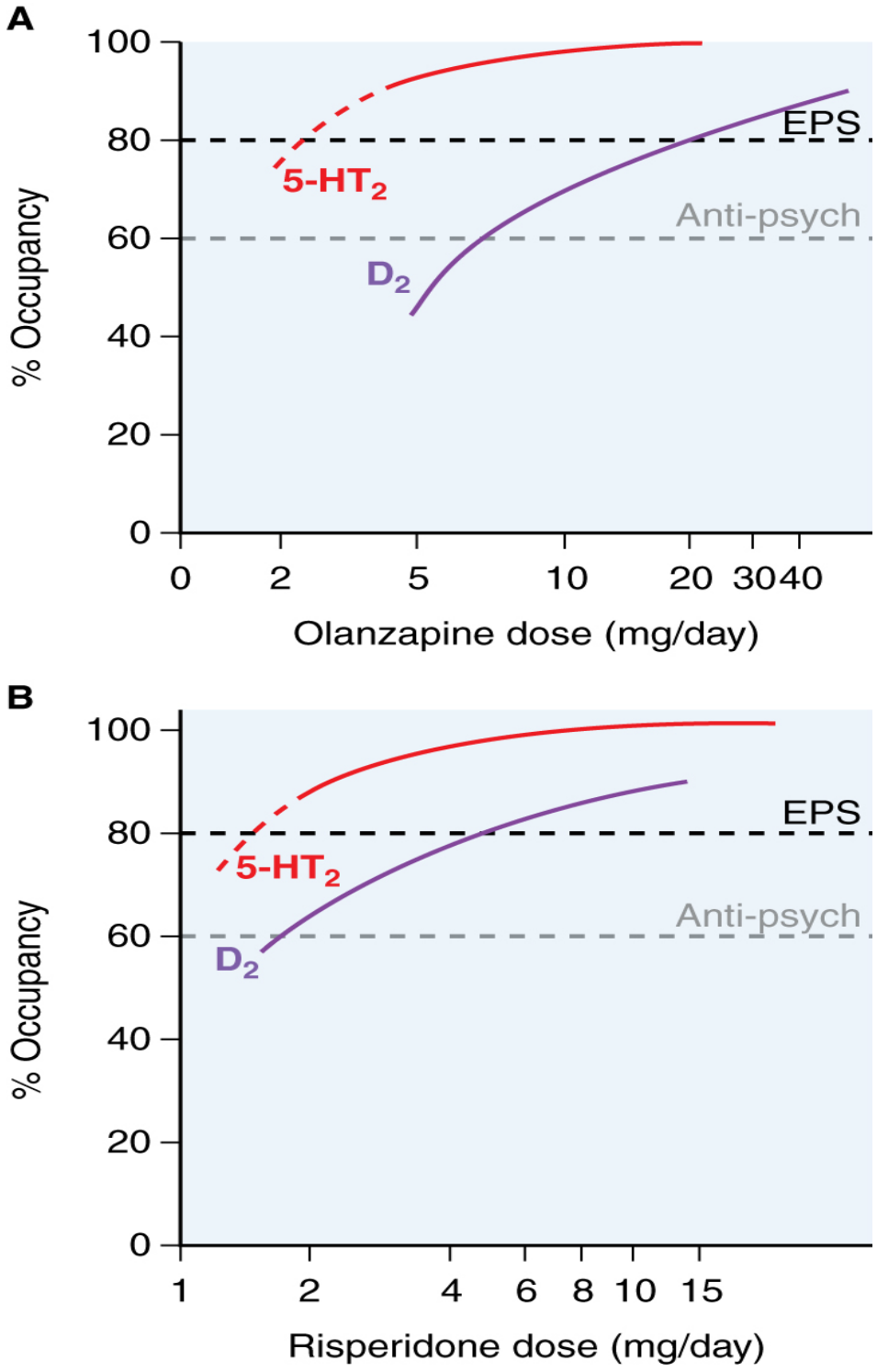


Figure (H): Receptor occupancy & clinical response of antipsychotics



SUSPECTED ADVERSE DRUG REACTION REPORTING FORM

For VOLUNTARY reporting of Adverse Drug Reactions by healthcare professionals

CDSCO
Central Drugs Standard Control Organization
Directorate General of Health Services,
Ministry of Health & Family Welfare, Government of India,
FDA Bhavan, ITO, Kotla Road, New Delhi
www.cdsco.nic.in

(AMC/ NCC Use only
AMC Report No.
Worldwide Unique no.

A. Patient Information

1.Patient Initials _____

2.Age at time of Event or date of birth

---

3. Sex ☐M ☐ F

4. Weight ____Kgs

12. Relevant tests / laboratory data with dates

B .Suspected Adverse Reaction

5. Date of reaction stated (dd/mm/yyyy)

6. Date of recovery (dd/mm/yyyy)

7. Describe reaction or problem

13. Other relevant history including pre-existing medical conditions (e.g. allergies, race, pregnancy, smoking, alcohol use, hepatic/ renal dysfunction etc)

14. Seriousness of the reaction

- ☐ Death (dd/mm/yyy)____
- ☐ Life threatening
- ☐ Hospitalization-initial or prolonged
- ☐ Disability
- ☐ Congenitial anomaly
- ☐ Required intervention to prevent permanent impairment / damage
- ☐ Other (specify)

15. Outcomes

- ☐ Fatal
- ☐ Recovering
- ☐ Unknown
- ☐ Continuing
- ☐ Recovered
- ☐ Other (specify)____

C.Suspected medication(s)

S.No	8. Name (brand and /or generic name)	Manufacturer (if known)	Batch No./ Lot No. (if known)	Exp. Date (if known)	Dose used	Route used	Frequency	Therapy dates (if known give duration)		Reason for use of prescribed for
								Date started	Date stopped	
i.										
ii.										
iii.										
iv.										

Sl.No As per C	9. Reaction abated after drug stopped or dose reduced					10. Reaction reappeared after reintroduction				
	Yes	No	Unknown	NA	Reduced dose	Yes	No	Unknown	NA	If reintroduced dose
i.										
ii.										
iii.										
iv.										

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

D. Reporter (see confidentiality section in first page)

16. Name and Professional Address :_____
_____
Pin code : _____ E-mail _____
Tel. No. (with STD code): _____
Occupation _____Signature _____

17. Causality Assessment

18. Date of this report (dd/mm/yyyy)

ADVICE ABOUT REPORTING

- **Report adverse experiences with medications**
- **Report serious adverse reactions. A reaction is serious when the patient outcome is:**

  - death
  - life-threatening (real risk of dying)
  - hospitalization (initial or prolonged)
  - disability (significant, persistent or permanent
  - congenital anomaly
  - required intervention to prevent permanent impairment or damage

- **Report even if:**

  - You're not certain the product caused adverse reaction
  - you don't have all the details, however, point nos. **1, 5, 7, 8, 11, 15, 16 & 18** (see reverse) are essentially required.

- **Who can report:**

  - Any health care professional (Doctors including Dentists, Nurses and Pharmacists)

- **Where to report:**

  - Please return the completed form to the nearest ***Adverse drug reaction Monitoring Centre (AMC)*** or to ***National Coordinating Centre***
  - A list of nationwide AMCs is available at: http://cdsco.nic.in/pharmacovigilance.htm

- **What happens to the submitted information:**

  - Information provided in this form is handled in strict confidence. The causality assessment is carried out at Adverse Drug Reaction Monitoring Centres (AMCs) by using WHO-UMC scale. The analyzed forms are forwarded to the National Coordinating Centre through the ADR database. Finally the data is analyzed and forwarded to the Global Pharmacovigilance Database managed by WHO Uppsala Monitoring Center in Sweden.

  - The reports are periodically reviewed by the National Coordinating Centre (PvPI). The information generated on the basis of these reports helps in continuous assessment of the benefit-risk ratio of medicines.

  - The information is submitted to the Steering Committee of PvPI constituted by the Ministry of Health and Family Welfare. The Committee is entrusted with the responsibility to review the data and suggest any interventions that may be required.

Suspected Adverse Drug Reaction Reporting Form

For VOLUNTARY reporting
of suspected adverse drug reactions by
health care professionals

Central Drugs Standard Control Organization
Directorate General of Health Services,
Ministry of Health & Family Welfare, Government of India
FDA Bhawan, ITO Kotla Road, New Delhi – 110002
www.cdsco.nic.in

Pharmacovigilance Programme of India for Assuring Drug Safety

Pharmacovigilance Programme of India (PvPI)

National Coordinating Centre,
Indian Pharmacopoeia Commission
Ministry of Health & Family Welfare,
Govt. of India
Sector-23, Raj Nagar, Ghaziabad-201 002.Tel.:0120-2783400, 2783401, 2783392, FAX: 0120-2783311
E.mail: ipclab@vsnl.net

Confidentiality: The patient's identity is held in strict confidence and protected to the fullest extent. Programme staff is not ex- pected to and will not disclose the reporter's identity in response to a request from the public. **Submission of a report does not constitute an admission that medical personnel or manufacturer or the product caused or contributed to the reaction**.

Version 1.0

MEDICINES SIDE EFFECT REPORTING FORM (FOR CONSUMERS)

Indian Pharmacopoeia Commission, National Coordination Centre- Pharmacovigilance Programme of India, Ministry of Health & Family Welfare, Government of India.

This reporting is voluntary, has no legal implication and aims to improve patient safety. Your active participation is valuable.

1.Patient Details

Patient Initials: ☐☐	Gender (√): Male ☐ Female ☐ Other ☐	Age (Year or Month) :

2. Health Information

a. Reason(s) for taking medicine(s)(Disease/Symptoms):

b. Medicines Advised by (√): Doctor ☐ Pharmacist ☐ Friends/Relatives ☐ Self (Past disease experienced/No past disease experienced) ☐

3. Details of Person Reporting the Side Effect

Name (Optional):

Address:

Telephone No:	Email:

4. Details of Medicine Taking/Taken

Name of Medicines	Quantity of Medicines taken (e.g. 250 mg, Two times a day)	Expiry Date of Medicines	Date of Start of Medicines	Date of Stop of Medicines
			dd/mm/yy	dd/mm/yy
			dd/mm/yy	dd/mm/yy
			dd/mm/yy	dd/mm/yy

Dosage form (√) : Tablet ☐ Capsule ☐ Injection ☐ Oral Liquids ☐ If Others (Please Specify.....)

5. About the Side Effect

When did the side effect started? dd/mm/yy Side Effect Continuing (Yes/No): ☐

When did the side effect stopped? dd/mm/yy

6.How bad was the Side Effect? (Please √ the boxes that Apply)

☐ Did not affect daily activities	☐ Affect daily activities
☐ Admitted to hospital	☐ Death
☐ Others	

7.Describe the Side Effect (What did you do to manage the side effect?)

The information provided in this form will be forwarded to ADR Monitoring Centre for follow-up. You are requested to cooperate with the programme officials when they contact you for more details. Please do report if you do not have all the information.

Please turn the page to read the instructions

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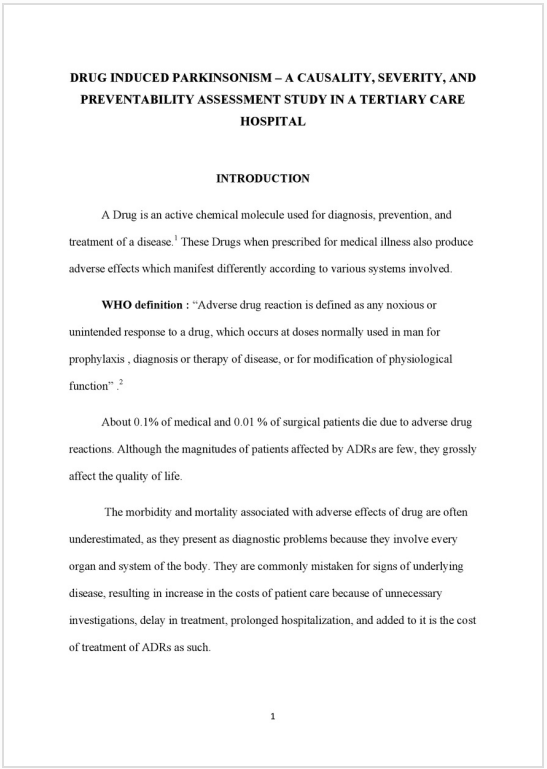

DRUG INDUCED PARKINSONISM – A CAUSALITY, SEVERITY, AND PREVENTABILITY ASSESSMENT STUDY IN A TERTIARY CARE HOSPITAL

INTRODUCTION

A Drug is an active chemical molecule used for diagnosis, prevention, and treatment of a disease.[1] These Drugs when prescribed for medical illness also produce adverse effects which manifest differently according to various systems involved.

WHO definition : "Adverse drug reaction is defined as any noxious or unintended response to a drug, which occurs at doses normally used in man for prophylaxis , diagnosis or therapy of disease, or for modification of physiological function" .[2]

About 0.1% of medical and 0.01 % of surgical patients die due to adverse drug reactions. Although the magnitudes of patients affected by ADRs are few, they grossly affect the quality of life.

The morbidity and mortality associated with adverse effects of drug are often underestimated, as they present as diagnostic problems because they involve every organ and system of the body. They are commonly mistaken for signs of underlying disease, resulting in increase in the costs of patient care because of unnecessary investigations, delay in treatment, prolonged hospitalization, and added to it is the cost of treatment of ADRs as such.

1

நோயாளி ஒப்புதல் படிவம்

ஆராய்ச்சியின் விவரம்:

ஆராய்ச்சி மையம்:

நோயாளியின் பெயர்: நோயாளியின் வயது:

பதிவு எண்:

நோயாளி கீழ்கண்டவற்றுள் கட்டங்களை (✓) செய்யவும்

1. மேற்குறிப்பிட்டுள்ள ஆராய்ச்சியின் நோக்கத்தையும் பயனையும் முழுவதுமாக புரிந்துகொண்டேன். மேலும் எனது அனைத்து சந்தேகங்களையும் கேட்டு அதற்கான விளக்கங்களையும் தெளிவுபடுத்திக் கொண்டேன். ☐

2. மேலும் இந்த ஆராய்ச்சிக்கு எனது சொந்த விருப்பத்தின் பேரில் பங்கேற்கிறேன் என்றும், மேலும் எந்த நேரத்திலும் எவ்வித முன்னறிவிப்புமின்றி இந்த ஆராய்ச்சியிலிருந்து விலக முழுமையான உரிமை உள்ளதையும், இதற்கு எவ்வித சட்ட பிணைப்பும் இல்லை என்பதையும் அறிவேன். ☐

3. ஆராய்ச்சியாளரோ, ஆராய்ச்சி உதவியாளரோ, ஆராய்ச்சி உபயத்தாரோ, ஆராய்ச்சி பேராசிரியரோ, ஒழுங்குநெறி செயற்குழு உறுப்பினர்களோ எப்போது வேண்டுமானாலும் எனது அனுமதியின்றி எனது உள்நோயாளி பதிவுகளை இந்த ஆராய்ச்சிக்காகவோ அல்லது எதிர்கால பிற ஆராய்ச்சிகளுக்காகவோ பயன்படுத்திக்கொள்ளலாம் என்றும், மேலும் இந்த நிபந்தனை நான் இவ்வாராய்ச்சியிலிருந்து விலகினாலும் தகும் என்றும் ஒப்புக்கொள்கிறேன். ஆயினும் எனது அடையாளம் சம்பந்தப்பட்ட எந்த பதிவுகளும் (சட்டபூர்வமான தேவைகள் தவிர) வெளியிடப்படமாட்டாது என்ற உறுதிமொழியின் பெயரில் இந்த ஆராய்ச்சியிலிருந்து கிடைக்கப்பெறும் முடிவுகளை வெளியிட மறுப்பு தெறிவிக்கமாட்டேன் என்று உறுதியளிக்கின்றேன். ☐

4. இந்த ஆராய்ச்சிக்கு நான் முழுமனதுடன் சம்மதிக்கின்றேன் என்றும் மேலும் ஆராய்ச்சிக் குழுவினர் எனக்கு அளிக்கும் அறிவுரைகளை தவறாது பின்பற்றுவேன் என்றும் இந்த ஆராய்ச்சி காலம் முழுவதும் எனது உடல் நிலையில் ஏதேனும் மாற்றமோ அல்லது எதிர்பாராத பாதகமான விளைவோ எற்படுமாயின் உடனடியாக ஆராய்ச்சி குழுவினரை அணுகுவேன் என்றும் உறுதியளிக்கின்றேன். ☐

5. இந்த ஆராய்ச்சிக்குத் தேவைப்படும் அனைத்து மருத்துவப் பரிசோதனைகளுக்கும் ஒத்துழைப்பு தருவேன் என்று உறுதியளிக்கின்றேன். ☐

6. இந்த ஆராய்ச்சிக்கு யாருடைய வற்புருத்தலுமின்றி எனது சொந்த விருப்பத்தின் பேரிலும் சுயஅறிவுடனும் முழுமனதுடனும் சம்மத்திக்கின்றேன் என்று இதன் மூலம் ஒப்புக்கொள்கிறேன். ☐

நோயாளியின் கையொப்பம் / பெருவிரல் கைரேகை ஆராய்ச்சியாளரின் கையொப்பம்

இடம்: தேதி: