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A Review Article on the Incidence of Adverse Drug Reactions in the Treatment of Various Psychiatric Conditions

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ABSTRACT

WHO (World Health Organization) defines an adverse drug reaction as, "drug which produce noxious and unintended effect on patient, which occurs in normal doses used in patient for prophylaxis, diagnosis "or on the other hand treatment of sickness or for the change of physiological capacities." WHO has dispatched Pharmacovigilance or Adverse medication response checking in the time of 1960s". It has been established for early detection and prevention of possible drug toxicity, drug oriented problems, morbidity and mortality, and also helps in the improvement of assent and also helps in the reduction of cost of therapy. Pharmacovigilance is the study of pharmacological science that deals with the collection, detection, assessment, monitoring and prevention of adverse effects of drugs or any other drug oriented problems. It acts as a key factor for the effective drug therapy, clinical practice and epidemiology. A psychosis is a mental illness due to various causative factors and is characterized by an incoherent action from the actuality. The effective maintenance therapy for bipolar, psychoses, mania, schizophrenia and etc., psychiatric condition are "Antipsychotic drugs", which are chemically diversified but have the unique in the palliative care of psychiatric symptoms. There is a chance of occurring extensive adverse drug reactions and this may lead to diminish the quality of patient life, extra pyramidal aliments which influence to interrupt the therapy, and also lead to fatal in maximum cases. In order to determine safe and effective treatment with lower risk of adverse drug reactions, there is a need of proficiency in appraisal of Adverse drug reactions due to Anti psychotic drugs by the clinicians. Now a days, monitoring and reporting of Adverse drug reactions become underprivileged. To overcome paucity in Adverse drug reaction monitoring and reporting informations, there is a demand for energetic scrutiny system in medical practice.

KEYWORDS: Adverse drug reaction, Pharmacovigilance, Antipsychotic drugs, Role of clinical pharmacist.

I. INTRODUCTION

World Health Organization(WHO) defines an adverse drug reaction as, "drug which produce noxious and unintended effect on patient, which occurs in normal doses used in patient for prophylaxis, diagnosis "or on the other hand treatment of sickness or for the change of physiological capacities."[1] WHO has dispatched Pharmacovigilance or Adverse medication response checking in the time of 1960s." It has been established for early detection and prevention of possible drug toxicity, drug oriented problems, morbidity and mortality, and also helps in the improvement of assent and also helps in the reduction of cost of therapy. [2],[3] Pharmacovigilance is the study of pharmacological science that deals with the collection, detection, assessment, monitoring and prevention of adverse effects of drugs or any other drug oriented problems. It acts as a key factor for the effective drug therapy, clinical practice and epidemiology.[3] A psychosis is a mental illness due to various causative factors and is characterized by an incoherent action from the actuality. The effective maintenance therapy for bipolar, psychoses, mania, schizophrenia and etc., psychiatric condition are "Antipsychotic drugs", which are chemically diversified but have the unique in the palliative care of psychiatric symptoms.[4] There is a chance of occurring extensive adverse drug reactions and this may lead to diminish the quality of patient life, extra pyramidal aliments which influence to interrupt the therapy, and also lead to fatal in

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maximum cases.[5] In order to determine safe and effective treatment with lower risk of adverse drug reactions, there is a need of proficiency in appraisal of ADRs due to Anti psychotic drugs by the clinicians.[6] Hence, a effort has been made to reveal update analysis of adverse drug reactions in this article. Also, an outlook of psychotic disorder and guidance to overcome ADRs and need of clinical pharmacist in the health care sectors.

PSYCHOTIC DISORDER:

A Psychosis is a mental illness due to various factors and is characterized by an incoherent action from the actuality.[4] They behave as a coarse person and severe disability in their social life. They loss their ability to reason, judge and response towards actions are lost. It is characterized by attention disability, mood swings, anomalous responses, depressive cognition, delusion and hallucination.[7] It is divided into two disorders. They are,

Cognitive disorder : It is also called neurocognitive disorder. It consist of Acute and chronic brain syndromes with delirium and dementia with psychotic symptoms. Vital features are confusions, disorientation, defective memory, disorganized thought and coarse behavior.

Functional disorder: In this disorder, emotion, thought, reasoning and behavior are extremely altered from the normal but memory and attitude of the patient are maintained.

Psychotic disorders are categorized into group as Schizophrenia, Paranoid States, Mood disorder and neurosis.

SCHIZOPHRENIA:

Delusion, hallucination and lack of insight are the characteristic features for Schizophrenia. It may also consist of disturbance in their behavior, thought process and social activity. It is a disorder caused by functional impairment of the brain and is not caused due to any anatomical and pathological defect in the brain.

PARANOID STATES:

It is characterized by presence of delusion and hallucinations. One third of patient suffers due to this paranoid state of disorder. They also suffer due to Persecution and other fixed delusion.

MOOD DISORDER:

It is a set of psychiatric diseases, it is also called as mood disorder. It may manifest as Bipolar disorder: Mania and Depression.

NEUROSIS :

It is a mental disorder with lesser impairment in social and personality function. Hallucinations and delusions are absent. Examples, Anxiety, Phobic States, Obsessive compulsive disorder and etc.,.[8],[9]

PATHOPHYSIOLOGY:

There are different pathological reasons for the occurance of psychotic disorders. They involved factors for pathophysiology in Neurotransmitters, Genetic factors, Neurodevelopmental factors, and Autoimmune and inflammatory disorders with psychosis.

Neurotransmitter factor: The dopamin and glutamine pathways of hippocampus, midbrain, corpus striatum and prefrontal cortex of the brain gets altered neurotransmission and this alteration leads to the occurance of emergence of psychotic symptoms. This study effect is based on the excess synaptic levels of dopamine and glutamate and this leads to increased postsynaptic stimulation. This effects include deficiency of Gama aminobutyric acid (GABA) inhibitory interneurons and reduced functioning N-methyl D-aspartate (NMDA) and (NMDARs) glutamate receptors which are used in the alteration of inhibitory-excitatory balance of neural systems. The stimulated 5-hydroxytryptamine subtype 2A ($5\text{-}HT_{2A}$) is a etiology for the occurance of specific type of psychosis.

Genetic factors: There is no determined genetic markers and modes of heritance of psychotic disorder but there is a two general hypotheses. They are Common disease-common allele hypothesis and the Common disease-rare allele hypothesis.

Neurodevelopmental factors: It is involves maternal infections, drug toxicity, and nutritional deficiencies, birth complications, postnatal trauma, and other some factors involved in the development of risk of psychotic disorders.

Autoimmune and inflammatory disorders associate with psychosis: The development of autoimmune and inflammatory disorders associate with psychosis is due to auto antibodies stimulate or due to neurotransmitter blocking function in the brain, especially in the glutamate system.[10],[11],[12]

SYMPTOMS OF PSYCHOTIC DISORDERS:

TERMS TO BE KNOWN:

HALLUCINATION: It can affect any of the senses. The most commonly affected sense is auditory.

DELUSIONS: It is a fixed false beliefs and it consist of subtypes. They include Persecutory, erotomaniac, delusions of grandeur, or somatic.

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DISORGANIZTION: It is characterized by patient's behaviors, thought process and speech.
Example for disorganized speech: neologisms, clang speech, word salad and echolalia.
Example for disorganized behaviours: perseveration, echopraxia, dressing oddly for the setting, or other behaviours which seems to be odd to their present situation.
APATHY: It is a lack of interest, enthusiasm and concern.
AVOLITION: It is a lack of motivation or ability to do tasks or activities.
ANHEDONIA: It is a decreased ability to experience pleasure.
ASOCIALITY: It is a lack of socialization.

Symptoms of Schizophrenia:

Symptoms of Schizophrenia is classified into three types of symptoms. They are positive symptoms, negative symptoms and cognitive symptoms of Schizophrenia.

Positive symptoms: It consist of Hallucinations, delusions, disorganized behavior, agitation, hostility and ideas of reference.

Negative symptoms: It consist of Diminished emotional expression, avolition, alogia, anhedonia, asociality, affective flattening and social withdrawal.

Cognitive symtoms: It consist of concrete thinking, inattention, problems with memory, learning and executive function, and also disorganization.

Symptoms of Paranoid states:

It consist of presence of delusion and hallucinations. Among psychiatric patients, one third of patient suffers due to paranoid states.

Symptoms of Mood disorder:

Symptoms of Mania: It consist of reduced sleep, hyperactivity, violent behavior, elation and irritable mood.

Symptoms of Depression: It consist of loss of interest and joyful, guilt, sadness, self-destruction, functions decreased gradually in physical and mental behavior.

Symptoms of Neurosis:

Anxiety disorder: Worry, tension and uneasiness.
Phobic states: Fear for objects, person and situation etc.,.
Obsession disorder: Repetitive thought, repetitive images, repetitive hand washing.
Compulsion disorder: It also consist of repetitive actions of same behavior.
Reactive depression: Loss, blow to self-esteem or bereavement, but excessive or disproportionate.
Post-traumatic stress disorder: Distressing experiences like war, riots, earthquakes etc.,.

PHARMACOTHERAPY OF PSYCHIATRIC DISORDER:

The effective maintenance therapy for bipolar, psychoses, mania, schizophrenia and etc., psychiatric condition are "Antipsychotic drugs", which are chemically diversified but have the unique in the palliative care of psychiatric symptoms.[4] Antipsychotic drugs are classified into first generation and second generation drugs based on their potency of psychotic disorder in the patient.

FIRST GENERATION ANTIPSYCHOTICS:

The other names of first generation antipsychotic drugs are Conventional, Typical or Traditional antipsychotics. It is mainly used for movement disorders. It is classified into two category based on their potency as typical low potency and typical high potency first generation antipsychotic drugs. It acts on dopaminergic neuroreceptors. The list of drugs for each category are given following.

First Generation – Low potency Antipsychotics:
Chlorpromazine (100-800mg/day), Trifluprомazine (50-200mg/day), Thioridazine (100-400mg/day).

First Generation – High potency Antipsychotics
Fluphenazine (1-10mg/day), Haloperidol (5-20mg/day), Pimozide (2-6mg/day), Thiothixene (5-60mg/day).

SECOND GENERATION ANTIPSYCHOTIC DRUGS:

It is also referred as Atypical antipsychotics. Extrapyramidal symptoms are highly occurred while using second generation antipsychotic drugs than first generation antipsychotic drugs. It also accomplished with some side effects like weight gain, diabetics and hypercholesterolemia. It acts to block serotonin and dopamine receptors. The list of second generation antipsychotic drugs are as following, Aripiprazole (10-30mg/day), Clozapine (100-300mg/day), Molindone (50-70mg/day), Olanzapine (2.5-20mg/day), Quetiapine (50-400mg/day), Risperidone (2-8mg/day)[8],[9],[10]

Antipsychotic agents have a broad spectrum of therapeutic effect in the clinical field. There is a chance of occurring extensive adverse drug reactions and this may lead to diminish the quality of patient life, extra pyramidal aliments which influence to interrupt the therapy, and also lead to fatal in maximum cases.[5] Knowledge in Adverse effect of Antipsychotic drug is important to frame

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the safe and effective treatment and less and reduced risk of side effects by the psychiatrist. In order to determine safe and effective treatment with lower risk of adverse drug reactions, there is a need of proficiency in appraisal of ADRs due to Anti psychotic drugs by the clinicians.[6] Now a days, monitoring and reporting of ADR become underprivileged. To overcome paucity in ADR monitoring and reporting informations, there is a demand for energetic scrutiny system in medical practice. Hence, an effort has been taken in this article to present an updated analysis of Antipsychotic drug induced adverse drug reactions with a general outlook and guidelines to overcome the situation with the role of clinical pharmacist in that situation.

ADVERSE DRUG REACTION:

WHO (World Health Organization) defines an adverse drug reaction as, "drug which produce noxious and unintended effect on patient, which occurs in normal doses used in patient for prophylaxis, diagnosis " or then again therapy of affliction or for the difference in physiological limits." [1] Extrapyramidal symptoms are exhibited by the first generation antipsychotic drugs and it lead to tardive dyskinesia. The drug clozapine is withdrawn due to its agranulocytosis effect and it again get back to the market with the guideline of monitoring the count of white blood cells and other investigations.[13],[14] The risk of seizure involved in both the first and second generation antipsychotic drugs, it mainly depends upon the increased pharmacological action, increased drug dose. High risk of seizure is due to first generation antipsychotic drugs than second generation antipsychotic drugs. Among second generation antipsychotic drugs, clozapine has higher risk of seizure than resperidone.[15],[16] Antipsychotic drug induced adverse drug reactions are associated with the following,

Central Nervous System, Weight gain, Hyperprolactinemia, Sedation, Sexual dysfunction, Neuroleptic malignant syndrome, Cardiovascular, Seizures and Other side effects of anti-psychotic drugs and Anti-cholinergic effects due to Antipsychotic drugs.

Central Nervous system:

It is termed as Extra pyramidal symptoms which are arised in the central nervous system. The etiology of this extra pyramidal symptoms are due to the imbalance of neurotransmitters, hyperactivity of M4 Muscarinic cholinergic neurons, and hypoactivity of D2 Dopaminergic neurons. This begins within a few weeks of treatment or when the drug dose increased. Dopamine hyperactivity is caused by the treatment of first and second generation antipsychotic drugs and it leads to parkinsonism disease.[16],[17],[18] Extra pyramidal symptoms consist of four main symptoms, they are akathesia, acute dystonia, parkinsonism, and tardive dyskinesia.[19],[20]

Akathesia: It is a movement disorder and this symptoms occurs with the first three months of treatment of first generation anti-psychotic drugs.[21],[22] This symptoms is treated by reducing the dose of the given drugs or addition of Beta blockers or Anti-cholinergic drugs to the treatment.[21],[23],[24] The effective drugs added to the treatment of akathisia are Propranolol (upto160mg/day), Metoprolol (upto 100mg/day), and nadolol (upto 80mg/day).[25]

Dystonia: It is a prolonged muscle contraction occurs within 24-90 hours the intiation of antipsychotic drug adminitraiton or drug dosage increased.[26] The risk factors for this symptom are young age, family history with dystonia and history of drug abuse. If this symptoms left untreated, it become a life threatening.[27],[28],[29] It can be treated with Anticholinergic, Antihistamine, or Benzodiazepines. Diphenhydramine 50 mg given either IM or IV or Diazepam 5 to 10mg IV slowly, or Lorazepam 1 to 2mg IM. After the administration of drugs the relief from the symptoms occurs at 15 to 20minutes while given as IM or 5minutes while given as IV administration.[21],[23],25],[30],[31]

Tardive dyskinesia: This symptoms occurs due to the chronic antipsychotic therapy. It is defined as abnormal involuntary movements. It is nonreversible symptom even after discontinuation of the treatment. It involves the abnormal movements of Jerks, tics, tongue protruding, lips puckering and limb movements.[32],[33] This symptoms become worsen to interfering with chewing, speech, respiration, facial movements or swallowing. These movements get worsen with stress, reduce with sedation, and disappear with sleep. The risk factors involved are duration of therapy, higher dose, cumulative dose, age, diabetes mellitus, mood disorders and in gender especially female. Treatment for dyskinesia is using clozapine as the first line drug for patient with moderate to severe dyskinesias. It use abnormal Involuntary Movement Scale (AIMS) and Dyskinesia Identification System.[34],[35],[36] The prevalence of dyskinesia is less due to different design and

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methods for the investigation of dyskinesia.[37],[38],[23]

Parkinsonism: This parkinsonism occurs as Pseudoparkinsonism. It is identified by either of the occurance of following symptoms in the patients. They symptoms are, Tremor, Postural abnormalities, rigidity, Akinesia, bradykinesia or decreased motor activity. The etiology for the occurance of psedoparkinsonism are increased dose, age, and gender especially female.[39],[40] The additional risk factors are AIDS and pre-existing rigidity.[41],[42],[43] Symptoms of parkinsonism are seborrhea, sialorrhea, fatigue, weakness, hyperhidrosis, dysphagia and dysarthria occurs within 1 to 2 weeks after the antipsychotic drugs or drug dose increase. Pseudo parkinsonism with SGAs have low risk but when risperidone with >6mg/day is high risk. It is treated by reducing the dose of antipsychotic drugs or by administration of anticholinergic drugs.[44],[45] Anticholinergic drugs are contraindicated for elder patients due to the side effects of dry mouth, risk of glaucoma, and urinary retention.[46],[47]

Weight gain:

This is a common adverse effect occurs mainly in adults and children and it is not due to dose of Anti-psychotic drug. It rapidly increase and it is difficult to control.[37] It can reduce quality of life and morbidity and mortality in cardiovascular and cerebrovascular system. Compared to second generation antipsychotic drugs, first generation antipsychotic drugs have the high risk of weight gain.[48] High risk of weight gain with Clozapine and Olanzepine compared to other atypical drugs of antipsychotic drugs.[49],[50] The intermediate risk of weight gain with Resperidone, Sertindole, Zotepine and Paliperidone drugs.[51] Re-demographic variables, illness characteristics, history and current treatment are the factors for the risk of weight gain.[52]

Hyperprolactinemia:

It is a increased level of prolactin in patient due to the blockage of dopamine in the hypothalamus and it leads to galactorrhoea in male.[53] It occurs after the admission of Anti-psychotic drugs and it arises within a few weeks of initiation of treatment or arises due to increased drug dosage and it can also arises after a long term usage. The serum prolactin levels of patient should be monitored.[54]

Sedation:

It is caused due to the affinity towards Histamine H1 receptor.[22] It is overcome by reducing daily dose and prescribing doses to bedtime.[55]

Sexual dysfunction:

It is a common side effect for most of the patients and it results in poor medication adherence.[56] Second generation antipsychotic drugs and risperidone results in galactorrhea in both and gynecomastia in male.[48],[56]

Neuroleptic Malignant Syndrome:

It is a serious adverse effect in youngers. It is characterized by skin pallor, tachycardia, tachypnoea, and blood pressure. It is a rare syndrome but it is a life threatening syndrome, it occurs within first week of the treatment.[57],[58],[59]

Cardiovascular:

There is a changes in ECG as prolonged QT interval and orthostatic hypotension which are caused due to low potency first generation Antipsychotic drugs and second generation Antipsychotic drugs.[37],[53]

Seizures:

It is caused due to higher dose or rapid dose of Antipsychotic drugs. Antipsychotic drug has the higher risk of seizures. Among Antipsychotic drugs, Clozapine has the highest risk of seizure.[8]

Other side effects of Antipsychotic drugs:

There are some other side effects caused by Antipsychotic drugs. They are hepatic failure, pancreatitis, heat stroke, nausea, colitis, constipation, fever, hypersalivation. Constipation is caused most commonly by Clozapine. It is a severe side effect. If it gets severe, it may lead to ileum, bowel occlusion and may also lead to death.[60-63]

Anti-Cholinergic effects:

It is caused due to low potency first generation antipsychotic drugs and especially clozapine with the effects of constipation, urinary retention, dry mouth, blurred vision.[64],[65],[66]

II. DISCUSSION:

IMPLICATION AND MANAGEMENT:

The ADRs information are varies among studies. These are the helpful points for the management of ADRs. They are,

- Clinicians need to capable mindful pretty much all the ADRs which are related from antipsychotic drugs.
- The need to offset the likely dangers with expected advantages must be remembered by clinicians.
- Treatment is individualized according to persistent premise, for example, finding, age, actual status, different variables like co-

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morbid conditions, other history of prescriptions, tolerant past reaction, wholesome status, etc.

- Clinicians ought to be remember that medicine solution ought to be joined by proper gadget.
- At the point when a patient on antipsychotic drugs, successive evalution of metabolic boundaries, ECG need to be done.
- At last, remember a current writing of patients will help a clinicians better figure a treatment plan, foresee possible issue, and maintained a strategic distance from them.

ROLE OF CLINICAL PHARMACIST:

Clinical drug specialists can screen results and subsequently improve consistence by inquisitive about sure and nefative side effects when the patient reorders medical care experts about changes in manifestations. Notwithstanding guaranteeing the right dosing of fitting medications, clinical drug specialists are key in managing patients about where they can acquire further assistance(model: through individual or gathering treatment).

Guidelines for ADRs Management:

i) Dose reduction: At the point, when an antipsychotic drug gave advantage to the patients about the occurance of ADRs and it is due to dose-dependent. Thus, the least portion is endorsed to the patients for accomplishing treatment objectives.

ii) Change to an antipsychotic drug: It tends to be applicable when the dose change cannot be demonstrated useful for the patients and tended to a hazardous or lethal.

iii) Prescription of Non-pharmacological intervention: It demonstrated successful when weight acquire and related lipid anomaly was tended to in this way, the eating routine and exercise programs are powerful.

iv) Treatment along with concomitant medication: These are utilized for lessening the ADRs which is related by antipsychotic tranquilizes yet they additionally have own antagonistic impacts. Thus, barely any attendant medicine approaches are upheld by prood from randomized controlled preliminaries.

III. CONCLUSION:

Even of ADR had generally influence Hospital stay of persistence in a roundabout way affecting financial weight on patients. ADR are frequently inadequately recognized and announced in everyday clinical practice. As we gathered all the more increasingly more data about ADRs, we need a functioning observation framework with respect to recognizable proof and revealing of ADRs with antipsychotic drugs. Specialist and clinical drug specialist are should have been made mindful of these possibly deadly unfriendly impacts related with antipsychotic drugs by means of associations of patient advising, quality based workshops, distributed clinical writing, gatherings, learning projects and Healthcare camps.

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