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REVIEW ARTICLE **OPEN ACCESS**

Neuropsychiatric Disorders: A Pharmacovigilance Perspective

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ABSTRACT
Pharmacovigilance as defined by World Health Organization (WHO) is the science and activities related to the detection, assessment, understanding, and prevention of adverse drug effects. Neuropsychiatry is the subspecialty of psychiatry that deals with disorders at the intersection of neurology and psychiatry. Patients with neuropsychiatric disorders are often treated with a combination of several drugs that contribute to Adverse Drug Reactions (ADRs). Further, due to exclusion of co-morbid medical conditions and short time duration of clinical trials, less reporting of ADRs during clinical trials of neuropsychiatric disorders has been observed. In such conditions, to monitor drug safety in neuopsychiatry, it is important to efficiently manage spontaneous ADR reports. For this, relevant articles of Pharmacovigilance and neuropsychiatric disorders were shortlisted. We searched PubMed for articles about pharmacovigilance in relation to 17 neuropsychiatric disorders. We searched for review as well as research articles applying filters like 2009-2019, using MeSH terms and text words. We identified four disorders viz. Alzheimer's Disease (AD), Epilepsy, Parkinson's Disease (PD), and Schizophrenia for our study and overall, 51 articles were considered potentially relevant out of a total of 212 articles; inclusive of reviews and research papers. Pharmacovigilance in neuropsychiatry must be highlighted with every effort, to improve safety and offer patients every possible help to improve their quality of life during such a critical period of their lives.
Keywords: Adverse Drug Reactions, Pharmacovigilance, Alzheimer's Disease, Epilepsy, Parkinson's Disease, Schizophrenia

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INTRODUCTION

Neuropsychiatry is said to be a specialty of neurology in which it is considered that the disease generally originates from the nervous system and impairs the patient's ability to learn and affect the mental state. Neuropsychiatry includes those symptoms which lies in the grey zone between neurology and psychiatry such as impairment of attention, memory, and intelligence.(Figure 1)Patients with such neuronal and psychotic symptoms are sensitive to side effects of therapies as pharmacotherapy is mostly used in neuropsychiatric disorders. There are more chances of occurrence of adverse drug events(ADE), in such condition constant monitoring of symptoms and developing adverse event is necessary. Therefore reporting of ADEs associated with the specific drug is done through various methods of pharmacovigilance and systematic data is generated..[1][2][3][4]

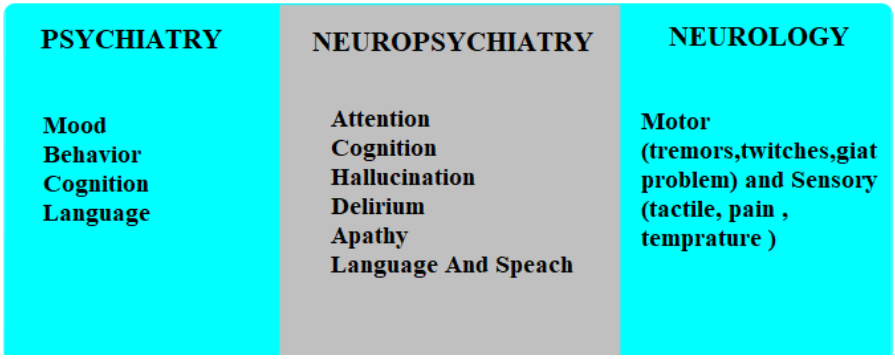

Fig. 1 Areas of Impaired Functioning in Neuropsychiatry[5]

Pharmacovigilance as defined by WHO "is the science and activities related to detection, assessment, understanding and prevention of adverse drug effect". Pharmacovigilance is activity to be carried out by the person involved in patient care that is doctors, nurses and pharmacist.
Studies found that 5% hospitalization of patient in an inpatient hospital was due to adverse drug reaction and 6.6% patient was seen that during treatment in hospital they developed adverse drug reaction and affected the treatment and hospital stay.
There are various reasons why pharmacovigilance is important in neuropsychiatric disorders:
Most of the psychiatric disorders are associated with neurological involvement as discussed above.The reason may be that in most of the psychiatric disorders pharmacotherapy is the first line treatment which is given and those drugs are associated with adverse drug reactions. It is seen that many patient require changes in therapy or using multiple drugs at a time (Polypharmacy)which may lead to adverse drug reaction or drug-drug interaction.
Another reason pharmacovigilance is important in neuropsychiatry is that during clinical trials of psychoactive drugs selection of patient is done by stringent criteria and the patients having various comorbidities are excluded, but in reality, these patients may have very complex situation with comorbidities which make it more prone to encounter adverse drug reactions.Also such trials are conducted for short period as compared with practically treating patients which may be longer or may requires long term treatment.[6]
As the major cause of symptoms and association with pathological changes in brain is mostly unknown therefore various long-term multiple drug therapies is used in treatment of neuropsychiatric disorders. According to WHO, neuropsychiatric diseases affects about 450 million people and such conditions are major cause of mortality worldwide.[7, 8]
As prevalence of neuropsychiatric diseases are increasing worldwide the need for pharmacovigilance studies and systematic reporting is also important for proper treatment and adverse event monitoring.
Alzheimer disease affects about 50 million people and there are 10 million new cases reported every year globally. Mostly older population are affected which leads to more dependency than other healthy aged population.[9]
Schizophrenia affects about 20 million people worldwide and is more disabling and also affects educational and occupational performance of the patient. Patients with schizophrenia are more likely to die due to other preventable diseases.[10]
In case of Parkinson disease it affects about 100 to 200 patients in 1 lakh of population and about 1% of population of above 60 years of age. Annual increase of the Parkinson disease worldwide is about 15 to 20 cases and this is gradually increasing.[11]
Compared to other neuropsychiatric disorders epilepsy is more prevalent around 65 million people are suffering with epilepsy worldwide. In developing and low income countries the affected population is estimated to be more than in developed countries almost 50 of 100,000 population in developed countries and around 700 per 100,000 in developing countries are detected.[12]

DISEASES

Epilepsy is a neurological disorder in which the cerebral excitability and inhibition of excited neurons is uncontrolled which results in in recurrent seizures.The treatment for epilepsy includes valproate, carbamazepine, lamotrigine,topiramate etc. These drugs cause some adverse drug reaction which lead to changes in treatment or other severe life threatening effects. These drugs shows various behavioral side effects which should be considered while selecting the drug. Various studies shows that it may lead to moderate to severe hypersensitivity reaction .While administering to pregnant for breastfeeding patients special attention should be given.[13, 14]
Alzheimer's disease is a common neurological disorder in which the presence of beta amyloid in plaques, formation of neurofibrillary tangles, accumulation of tau protein which leads to neurodegeneration and results in cognitive decline. Aggregation of such components in the neuron and synapse lead to degeneration and development of neuropsychiatric symptoms.
Various classes of drugs are used in treatment depending on the severity of the disorder (Donepezil, Rivastigmine) for moderate Alzheimer's disease NMDA receptor antagonist example Memantine can be used for severe Alzheimer's disease.In the drug used for treatment of nervous system the frequency was 3.3 % for anti-dementia drugs which shows occurrence of falls and neuropsychiatric disorders. Cholinesterase inhibitors were widely used earlier which shows Adverse drug reactions reported in various randomized clinical trials that most reported adverse drug reaction was GIT in 10% patients which includes nausea, vomiting, increased gastric acid secretion, and diarrhea. Other non GIT ADR's where tremors, bradycardia, hypotension or syncope.[15–17]

Schizophrenia is a chronic mental disorder that includes various symptoms such as hallucination, disorganized behavior, and lowering of cognitive ability. There are of two types of Symptoms negative and cognitive. Negative symptoms are characterized by loss of abilities. Cognitive symptoms includes memory loss, impairment in attention etc.First line of treatment for schizophrenia according to American psychiatric association, atypical antipsychotic except clozapine(because it causes agranulocytosis)are used. Due to less extrapyramidal symptoms second generation is preferred over first generation antipsychotics.Metabolic side effects such as weight gain, diabetes, hyperlipidemia have been associated with second generation antipsychotics which leads to increased risk of cardiovascular complications in schizophrenic patients.[18]

Parkinson's disease is a chronic neurodegenerative disease which shows both motor and non-motor symptoms.Motors symptoms such as resting tremors, muscle rigidity, bradykinesia which progresses and affects mobility and muscle control. These are due to loss of dopaminergic neurons.Non-motor symptoms are seen due to the loss of dopamine neurons in non-dopaminergicareas. This disease has an impact on patient families due to the increase of degenerative effects on muscle control. There are four classes of drugs for or treatment are dopamine precursor, dopamine agonist,inhibitors of catechol-o methyltransferase (COMT) and monoamine oxidase B (MAO-B). This type of drugs shows the same frequency of side effects and some drugs shows unique adverse effect which requires special attention. Long-term levodopa treatment leads to motor symptoms. Other side effects are sleep disorders gastrointestinal disturbance, edema, and other neuropsychiatric disorders.[19, 20]

RELEVANT ARTICLES FOUND ON PUBMED

For shortlisting articles relevant to Pharmacovigilance and neuropsychiatric disorders, we searched PubMed for articles about pharmacovigilance in relation to 17 neuropsychiatric disorders. We searched for review as well as research articles applying filters like 2009-2019, using MeSH terms and text words. We identified four disorders viz. Alzheimer's, Epilepsy, Parkinson's and Schizophrenia for our study and overall, 51 articles were considered potentially relevant out of a total of 212 articles inclusive of reviews and research papers. (Table 1)

Table 1 Relevant articles found on PubMed

Sr. no.	Keyword	PubMed	Relevant
1.	Pharmacovigilance Alzheimer's disease	40	17
2.	Pharmacovigilance Panic disorder	2	2
3.	Pharmacovigilance Epilepsy	60	25
4.	Pharmacovigilance Schizophrenia	54	25
5.	Pharmacovigilance Traumatic brain injury	4	0
6.	Pharmacovigilance Bipolar disorder	28	8
7.	Pharmacovigilance Cerebral vascular disease	22	4
8.	Pharmacovigilance Parkinson's disease	46	15
9.	Pharmacovigilance Brain tumors	14	9
10.	Pharmacovigilance Multiple sclerosis	77	37
11.	Pharmacovigilance Autism	9	5
12.	Pharmacovigilance Pick's disease	0	0
13.	Pharmacovigilance Huntington's disease	2	2
14.	Pharmacovigilance Narcolepsy	13	9
15.	Pharmacovigilance Wilson's disease	0	0
16.	Pharmacovigilance Prion diseases	0	0
17.	Pharmacovigilance neuropsychiatric disease	22	

From the shortlisted articles of Alzheimer's, Drugs used in treatment of Alzheimer's Disease and reported ADRwe studied the drug and associated adverse drug reaction reported in the articles are described in the following tables (Table 2-5) and Prismaflow diagram of the selection of studies is shown in Figures(Figures 2-5). All the reported ADRs are then classified according to the System Organ Class (SOC) (Table 6). The Distribution of ADR in specific disorder according to SOC is shown in Pie Charts (Figure 6-9).

Table 2 Drugs used in treatment of Alzheimer's Disease and reported ADR[16, 17, 21–27]

Sr no	Method	Drug	Reported ADR	Country
1	Search Database	Donepezil, Rivastigmine, Galanlarnine	Nausea, Vomiting , Bradycardia, Weight loss	France
2	VigiBase	Donepezil, Rivastigmine, Galantamine	Nausea and vomiting, Confusion, Diarrhoea, Bronchospasm, Dyspnea, Tremor, Urinary disorders, Muscle contractions and myoclonus,seizures, anxiety, aggressive behavior, and insomnia	
3	Search Database	Angiotensin-converting enzyme inhibitors, angiotensin receptor blockers ,and neuroleptic drugs	Neurologicaland psychological disorders, gastro-intestinal disorders,dermatological and allergic disorders, renal and urinary disorders, cardiovascular disorders, metabolic disorders , electrolyte imbalance, haemorrhagic events.	
4	Cross-sectional multicentre study	Rivastigmine, Donepezil, Galantamine	Gastro-intestinal, central nervous system and psychiatric disorders	France
5	Statistical analysis of the Food and Drug Administration Adverse Event Reporting System (FAERS) and the Canada Vigilance Adverse Reaction Database (CVARD)	Rivastigmine, Donepezil, Galantamine	Death, Pneumonia,Loss of Consciousness, Convulsion,Syncope	Canada,United States of America
6	VigiBase	Rivastigmine, Donepezil, Galantamine	Neuropsychiatric, gastrointestinal, general, and cardiovascular disorders, Death.	Europe and North America.
7	Search Database	Anticonvulsants	Neurological and psychological disorders	France
8	Retrospective analyses.	Donepezil and Memantine	Bradycardia , weakness andconvulsions	France
9	Analysis of French pharmacovigilance database	Cholinesterase inhibitor	CNS disorders, gastrointestinal disorders and cardiac rhythm disorders.	France

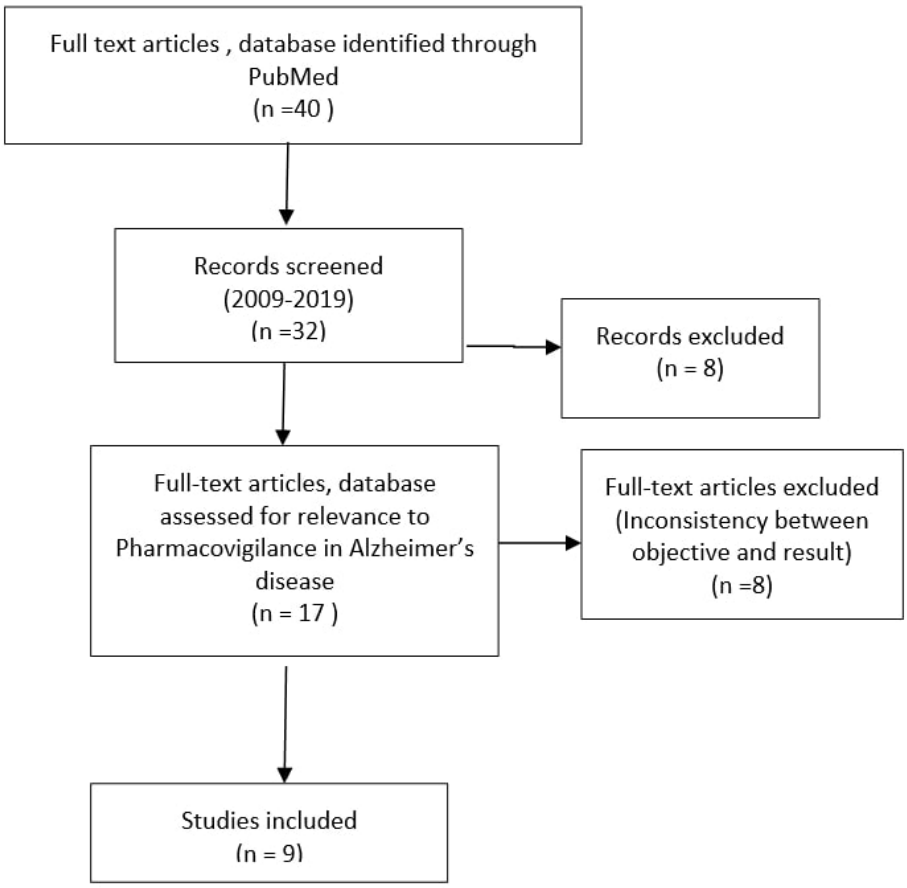

Fig 2 Flow diagram of the selection of studies for Alzheimer's Disease

Table 3 Drugs used in treatment of Parkinson's disease and reported ADR[28–37]

S. No.	Method	Drug	Reported ADR	Country
1	Literature review	Rotigotine and Pramipexole	Hiccups	Europe
2	Research Database	Levodopa	Polyneuropathy	UK
3	FDA Adverse Event Reporting System (FAERS)	Dopamine agonists	Behavioural addictions	USA
4	Spanish Pharmacovigilance System	Pramipexole	Gambling disorder	Spain
5	Spontaneous reporting	Aripiprazole, Entacapone/Benserazide, Carbidopa, Pergolide, Ropinirole, Rotigotine	Gambling disorder	Italy
6	MEDLINE	Quetiapine, Clozapine	Neuroleptic malignant syndrome	Spain
7	Vigibase	Pergolide	Heart failure	France
8	Retrospective cohort study	Co-administration of Rasagiline and an SSRI	Serotonin syndrome	Canada
9		Levodopa	Movement disorders gastrointestinal, psychiatric, and	
10	AnalysedAEcase line	Bromocriptine, Cabergolinc, Pergolide, Pramipexole and Ropinirole	Syncopal/pre- syncopal, fibrotic, psychotic, obsessive-compulsive behaviours and increased sleep	Australia

FDA Food and Drug Administration, *SSRI* Selective Serotonin Reuptake Inhibitor

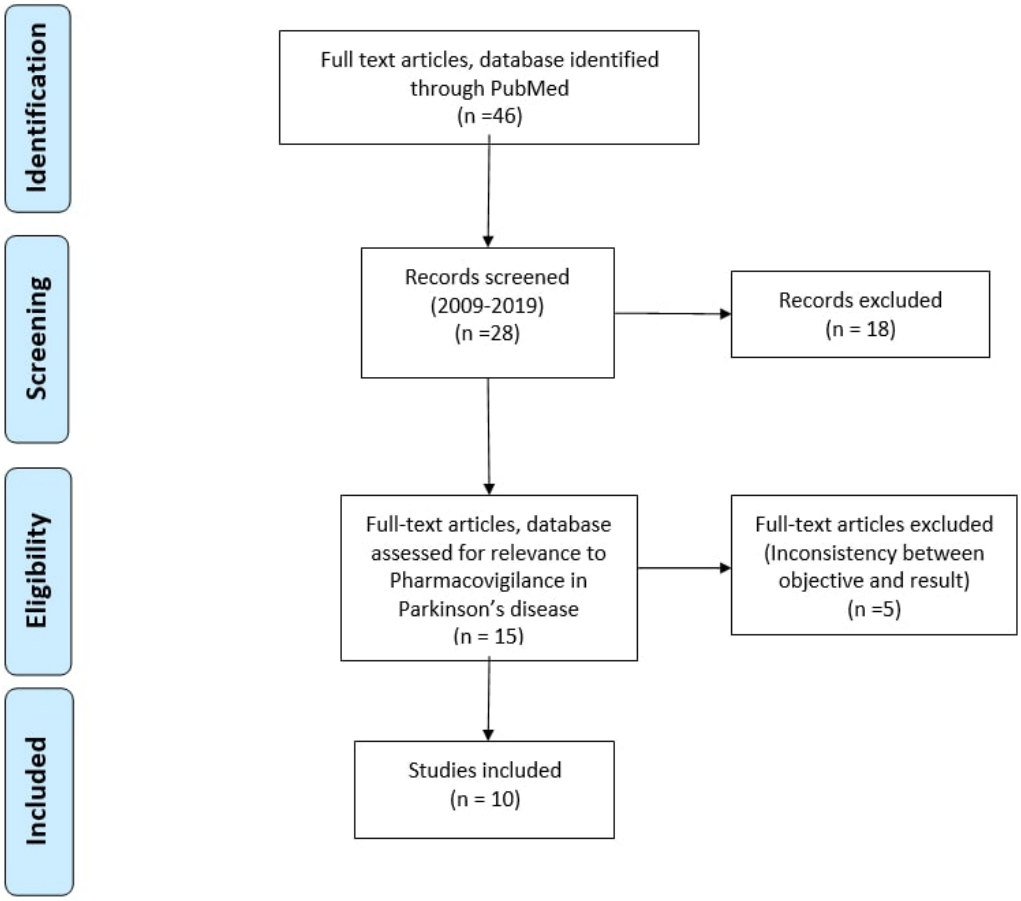

Fig. 3 Flow diagram of the selection of studies for Parkinson's Disease

Table 4: Drugs used in treatment of Epilepsy and reported ADR[14, 38–48]

S.N.	Method	Drug	ADR	Country
1	Case studies	Phenytoin sodium as a substitute for phenytoin base	Increase of seizure frequency, death	France
2	Retrospective study	Lamotrigine and Levetiracetam	Hyperammonemia	Japan
3	Case studies	Topiramate(mother)	Watery diarrhea(child)	Norway
4	Case Study	Phenobarbital	Hemophagocytosis syndrome	
S	Data mining analysis	Lamotrigine	Aseptic meningitis	USA
6	Cohort	Antiepileptic-drug treatment	Suicidality	UK
7	Case study	Oxcarbazepine	Hepatotoxicity(acute)	
8	Reviewed the data of outpatients	Carbamazepine , Valproate , Lamotrigine , Oxcarbazepine , Topiramate and Levetiracetam	Psychiatric disorders, neurological disorders and gastrointestinal disorders. Skin and appendage disorders, serious allergies, fetal malformations, renal calculus and pancreatitis	China
9	Vigibase	Valproic acid	Hyponatraemia	Netherlands
10	Case study	Clonidine	Consciousness deficit with drowsiness, , hypotonia and suspected generalized seizures hypotonia, and suspected generalized seizures neonatal hypotonia	France
11	Data analysis	Phenytoin	Hyperammonemia	Japan
12	Prospective cohort study	Pregabalin	Dizziness, somnolence, feeling drunk, fatigue, increased weight, Headache	Netherlands

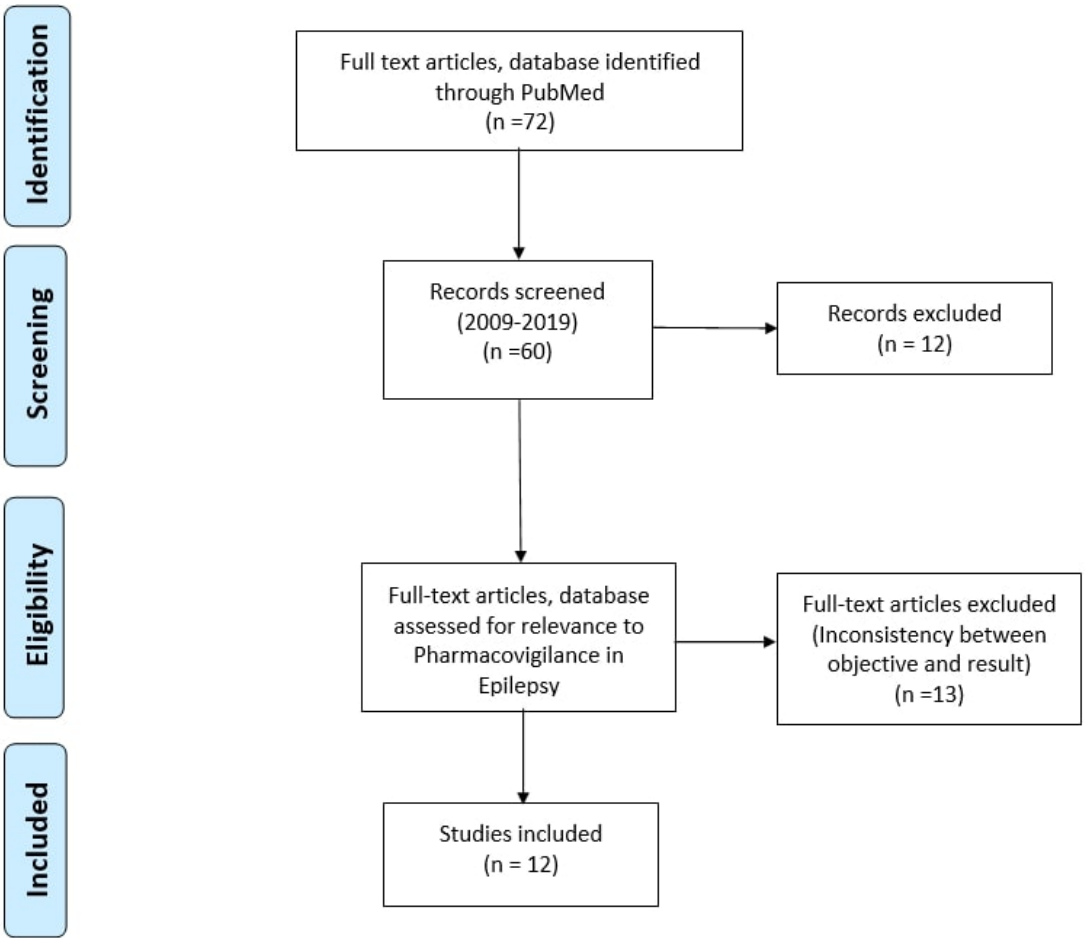

Fig. 4 Flow diagram of the selection of studies for Epilepsy

Table 5 Drugs used in treatment of Schizophrenia and reported ADR[37, 49–63]

S. N	Method	Drug	Reported ADR	Country
L	Review of reports	Clozapine	Gastrointestinal Hypomotility, constipation, ileus, bowel obstruction, and even death	Australia
2	Cross-sectional survey	Antipsychotics	Weight gain , gastro-intestinal , skin ,cardiovascular ,and sexual dysfunctions	India
3	Review of reports	Cariprazine	Akathisia , tremor, restlessness, weight gain	USA
4	MedDRA	Zyprexa(Olanzapine) Risperdal(Risperidone), Seroquel(Quetiapine), Abilify(Aripiprazole), Geodon(Ziprasidone)	Polycystic ovaries	Korea
5	Data from the Therapeutic Goods Administration	Clozapine	Neutropenia, myocarditis and cardiomyopathy .	Australia
6	Cohort study	Atypical antipsychotics	Fetal death	Tennessee US.
7	Inpatients data analysis	Ziprasidone and Olanzapine	Serum prolactin levels	China
8	Systematic	Bromocriptine and	Suppression of lactation	Australia

	review of the literature	Cabergoline		
9	Case study	Clozapine	Fetal heart rate alterations	France
10	Prospective observational study	Olanzapine long-acting injection	Post injection delirium/sedation syndrome (PDSS)	Australia, Austria, Belgium, Bulgaria. Croatia, Czech Republic, Denmark, Finland, France, Germany, Greece, Hungary. Ireland, Israel, Italy, Lithuania, New Zealand, Poland, Romania, Slovakia, Slovenia. Spain.
11	Randomized double-blind core study	Asenapine and Olanzapine.	Body weight increased and extrapyramidal effects	Netherlands
12	Review of the literature	Aripiprazole	Hypersexuality increased libido, unusual frequent masturbation and sexual instincts	France
13	Study cohorts	Clozapine	Agranulocytosis	UK. USA, and European countries
14	Cross-sectional Questionnaire-based telephone survey	Psychotropic Drugs	Impairments in the mouth, Jaw and face area	Germany.
15	Prospective Study of analysis	Risperidone and Olanzepine	Weight gain, dizziness, Sleep disturbance and appetite disturbance	India
16	Case report	Clozapine	Leukocytoclasticvasculitis (LCV),underlying infection, collagen Vascular disorders.	India

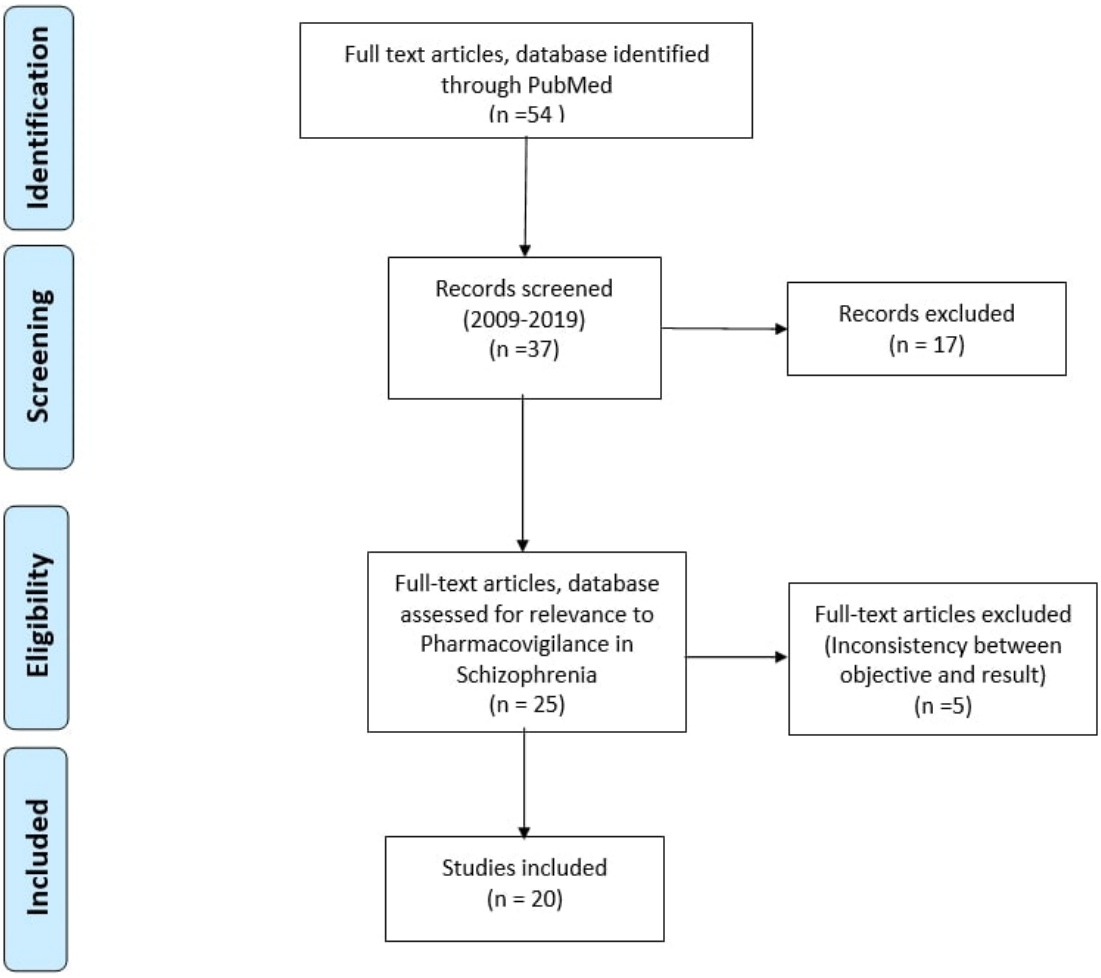

Fig 5 Flow diagram of the selection of studies for Schizophrenia

Table 6 Classification of ADRs Reported According to System Organ Class

SOC	Alzheimer's Disease	Parkinson's Disease	Epilepsy	Schizophrenia
Blood and lymphatic system disorders			Hemophagocytosis Syndrome	Agranulocytosis
Cardiac disorders	Bradycardia, Arrythmia	Heart failure		Myocarditis
Congenital, familial and genetic disorders			Fetal malformations	
Ear and labyrinth disorders				
Endocrine disorders				Hyperprolactinaemia
Eye disorders				
Gastrointestinal disorders	Vomiting		Watery diarrhea	
General disorders and administration site conditions				
Hepatobiliary disorders			Pancreatitis	

Immune system disorders	Allergic disorders		Serious allergies	Collagen vascular Disorders
Infections and infestations			Aseptic meningitis	
Injury, poisoning and procedural complications	Fall, Syncope		Hepatotoxicity	
Investigations				
Metabolism and nutrition disorders	Weightloss		Hyperammonemia Increased weight	
Musculoskeletal and connective tissue disorders	Muscle contractions, myoclonus	Movement disorders	Hypotonia, neonatal hypotonia	
Neoplasms benign, malignant and unspecified (incl cysts and Polyps)				Malignancy
Nervous system disorders	Nausea,Tremors, seizure insomnias, Loss of Consciousness, Convulsion	Polyneuropathy , Serotonin syndrome, Neuroleptic malignant Syndrome	Seizure, consciousness deficit with drowsiness, dizziness, somnolence,	Seizures
Pregnancy, puerperium and perinatal conditions				
Psychiatric disorders	Confusion, anxiety, Aggressive behavior	Behavioral Addictions, Gambling disorder	Suicidality, feeling Drunk,	
Renal and urinary disorders	Electrolyte imbalance		Renal calculus, Hyponatraemia	
Reproductive system and breast disorder				Hypersexuality Increased libido, unusual Frequent masturbation and sexual instincts
Respiratory, thoracic and mediastinal disorders	Bronchospasm and Dyspnea, Pneumonia	Fibrotic, synopal Fibrotic,hiccups		
Skin and subcutaneous tissue disorders				LeukocytoclasticVasculitis (LCV)
Social circumstances				
Surgical and medical procedures				
Vascular disorders				

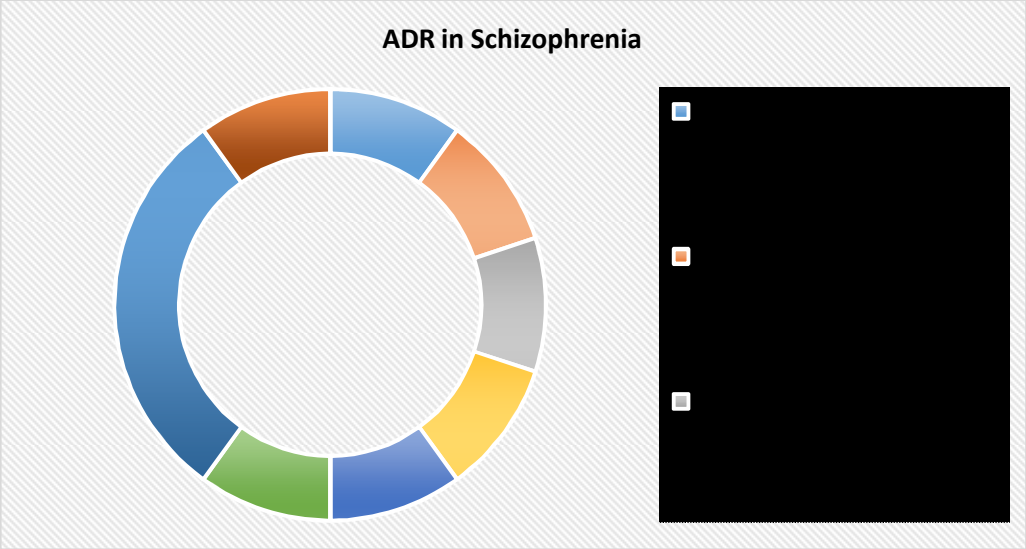

Fig 6 Distribution Adverse drug reactions in Schizophrenia

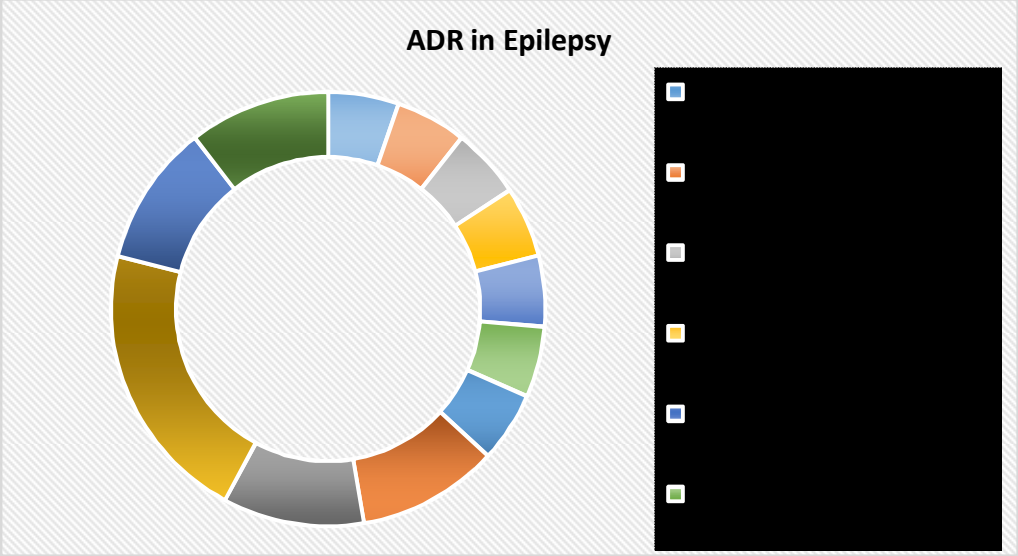

Fig 7 Distribution Adverse drug reactions in Epilepsy

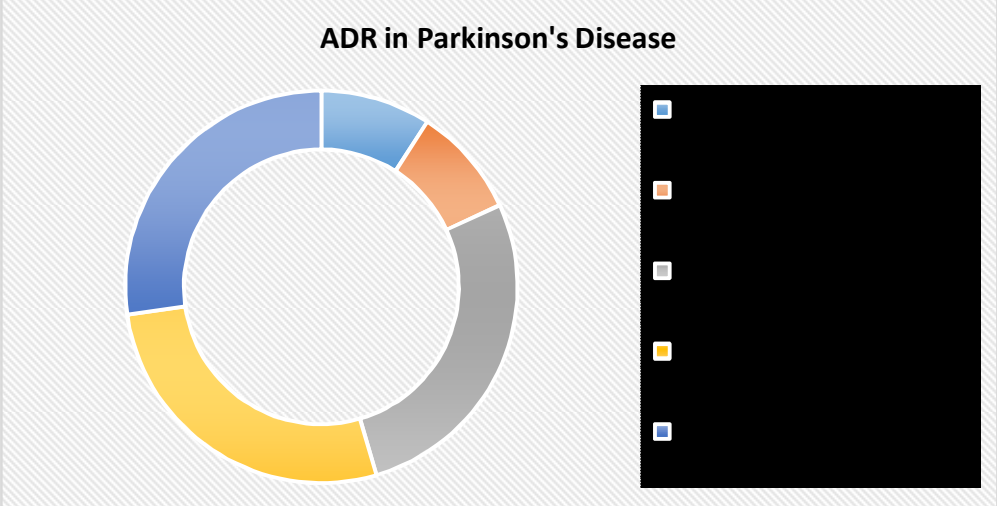

Fig 8 Distribution Adverse drug reactionsin Parkinson's Disease

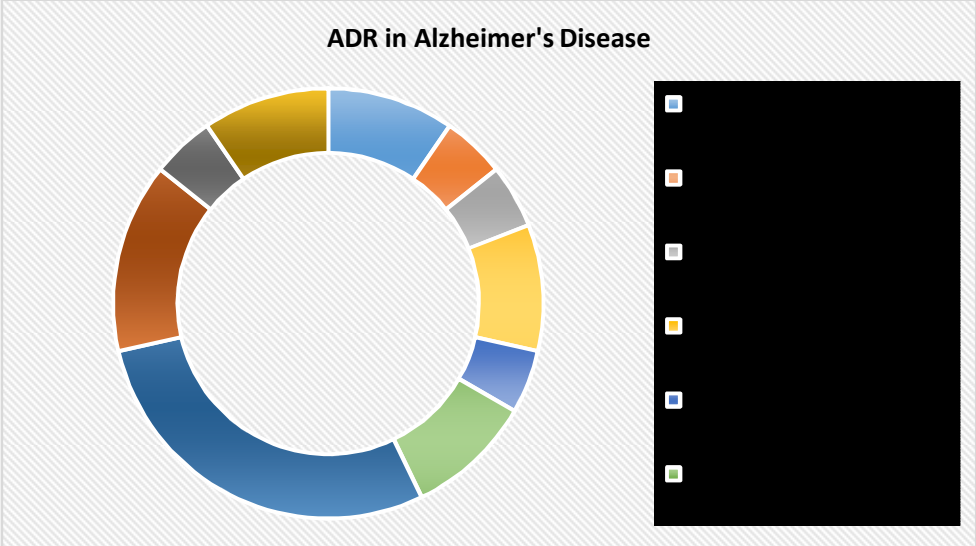

Fig 9 Distribution ADR in Alzheimer's Disease

DISCUSSION

Pharmacovigilance is the science and strategies in which the adverse drug event occurring during the treatment is detected and evaluated that is there any correlation between the adverse drug event and the drug administered. By using the modern pharmacovigilance techniques we can avoid epidemiological tragedies similar to that of thalidomide. In neuropsychiatric disorders, the association between the drug and the event is difficult as compared with other diseases since pharmacotherapy is mostly used, and also multiple drugs at a time are administered (polypharmacy). Also in most of the cases of neuropsychiatric patients they suffer many comorbidities therefore the distinguishing between the effect of the drug and the adverse event is difficult.During the treatment with drugs various reaction occurs which need not to be an ADR related with these drugs. To relate these reactions WHO has developed causality assessment scale and it can be also done by previously known Naranjo's algorithm.Therefore in the mid1990s International Council for Harmonisation (ICH) working group designed a standard database called MedDRA.

It is a terminologies database that is clinically validated and used by regulatory authorities and pharmaceutical companies in post marketing reporting of ADE using MedDRA in spontaneous reporting method pharmacovigilance and other methods so that proper causality assessment can be done. Thus by proper systematic reporting of ADR helps in developing different strategies by regulatory authorities and medical practitioners and reducing the cost of care and overall health of the patient.[64, 65]

CONCLUSION

The spontaneous reporting of ADRs is an important task for clinical pharmacists and other health professionals. Applying Pharmacovigilance in neuropsychiatry will enable physicians, pharmacists, clinicians, and other medical personnel to better diagnose and report adverse drug reactions.The efficient management of spontaneous ADR reports is essential to monitor drug safety in neuropsychiatry, where pharmacotherapy is de facto affected by a high prevalence of drug-related complications and a narrow therapeutic window. Clinical pharmacists qualified in pharmacovigilance have great responsibilities to promote safety, carefully follow neuropsychiatric patients in treatment, and support educational initiatives. It will help in detection, assessment, understanding, prevention, and further reporting of specific ADRs which have not been identified previously.

The importance of pharmacovigilance in neuropsychiatry must be highlighted with every effort, to improve safety and offer patients every possible help to improve their quality of life during such a critical period of their lives. Although, this study has been a review to investigate and report the various ADRs about neuropsychiatry, utilizing methods in PV, research into this domain is still warranted. A further aim of our study can be to target a specific patient population such as, infants, adults, pregnant, or the elderly. Also, by selecting an explicit treatment regimen or class of drugs, we can better identify, isolate and thereby treat the associated ADRs.

FUNDING

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COMPETING INTEREST

Authors Mohit Umare, Niyamat MA Chimthanawala, Rashmi V Trivedi, Nitu L Wankhede, Milind J Umekar, Mayur B Kale* declare that they have no conflict of interest.

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