



**International Journal of Biology, Pharmacy
and Allied Sciences (IJBPAS)**

'A Bridge Between Laboratory and Reader'

www.ijbpas.com

**PREVALENCE OF ADVERSE EFFECTS OF ANTI-EPILEPTIC DRUGS AT
TERTIARY CARE TEACHING HOSPITAL: AN OBSERVATIONAL STUDY**

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Received 15th June 2020; Revised 20th July 2020; Accepted 23rd Oct. 2021; Available online 1st July 2022

<https://doi.org/10.31032/IJBPAS/2021/11.7.6208>

ABSTRACT

A single Centre prospective observational study. Patients (<18 years old) receiving one or more AEDs for epilepsy, at each clinically determined follow-up visit. Primary outcome was adverse reactions of AEDs. Behavioral and cognitive functions were secondary outcomes. A total of 64 patients were recruited into this study. The median age of the patients was 26.2 years. A total of 47 patients were on polytherapy and 17 on monotherapy. Over half of the patients received either Levetiracetam or carbamazepine as monotherapy. Seventy-four per cent of all AED prescriptions were old generation drugs. The most frequently prescribed drugs were Levetiracetam (42%), (9%). Conclusion: In conclusion, polytherapy increases the possibility of ADRs in patients. Physicians should give AED polytherapy only when the maximum therapeutic doses of monotherapy are ineffective. Both clinicians and parents should monitor AED treated patients for adverse reactions, especially behavioral problems and somnolence. To assess the types of ADRs in prescribed drugs, Prevention and control the adverse effects of antiepileptic drugs, Risk and benefit related to antiepileptic drugs, improving health outcomes for epilepsy patients.

Keywords: Polytherapy, monotherapy, seizures, AED, ADR, Levetiracetam, carbamazepine, carbamazepine, lamotrigine, Sodium valproate

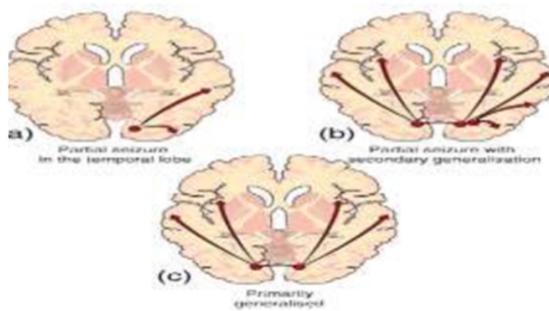
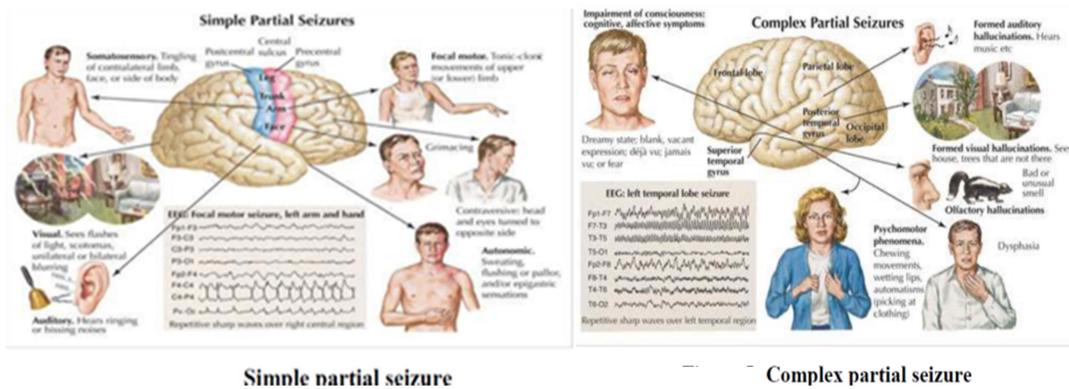
INTRODUCTION

The subject of the study is about the adverse drug reactions of antiepileptic drugs on patients. Designing a hospital-based study enabled to interview all the people in the hospital, who were identified to have epilepsy. According to W.H.O. epilepsy is the most common chronic brain disease and can affect the people of all age and if it is diagnosed and treated properly 70% of people with epilepsy can be free from seizure. They are the result of excessive electrical discharges in a group of brain cells¹. It is a transitory incidence of sign and symptoms due to uncharacteristic unnecessary or synchronous neuronal activity in the brain. Epilepsy is a disease differentiated by a continuingly predisposing to produce epileptic seizure and by neurobiological, cognitive, psychological and social consequences of this condition. Epilepsy is the fourth greatest, common neurological disorder and affects people of all ages. Aspect of epilepsy is recurrent, malicious seizures. A person is diagnosed with epilepsy if they have two unprovoked seizure. For the reason that epilepsy is caused by abnormal activity in the brain, seizure can affect any process of brain coordinates [1-2]. Epilepsy sign and symptoms may include: temporary confusion, uncontrollable jerking

movements of the arms and legs, a staring spell, loss of consciousness or awareness, extrasensory symptoms such as anxiety, fear. Epilepsy has no particular cause in about half people with this condition. In the other half the provision may be traced to various factors including head trauma, genetic influences, infectious diseases, brain conditions, prenatal injury, Developmental disorders etc. And the definite factors may increase the risk of epilepsy like age, head injuries, family history, stroke and vascular disease, brain infection, dementia, high fever etc. Doctors usually classify epilepsy as either generalized or focal, based on how the uncharacteristic brain activity begins. Focal seizures when seizures appear to end result from abnormal activity in just one area of your brain, they are called focal (partial) seizure. These seizure falls into two categories as focal seizure without loss of consciousness. And focal seizures with impaired attentiveness Generalized seizures when seizures that appear to involve all areas of the brain are called generalized seizure. Six types of generalized seizures exist- tonic seizures, absence seizures, tonic seizures, myoclonic seizures, clonic seizures, tonic-clonic seizures [2]. Having seizures at definite times can lead to circumstances that are hazardous

are drawing, falling, car accidents, etc. [4-5]. Other life frightening obstacles of epilepsy are rare but may occur such as status

epilepticus, sudden unexpected death in epilepsy [8].



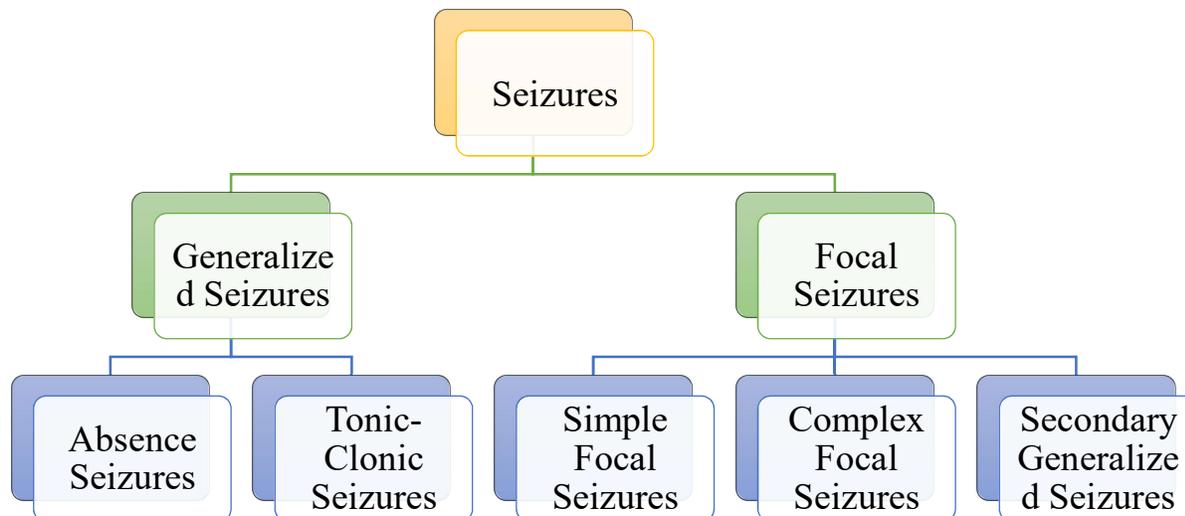
Secondary Generalized Seizure



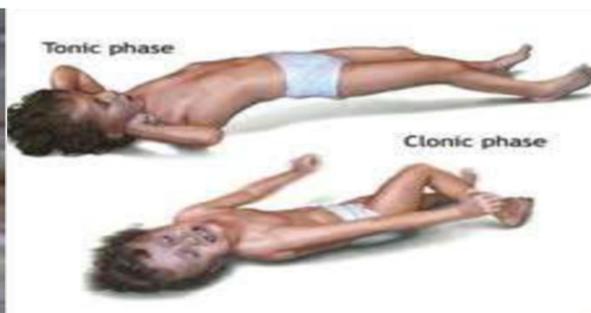
Absence Seizure

The main purposes of the study were to carry out adverse drug reaction among epileptic patients attending the tertiary care hospital. The implication of the study is to find risk factors of epilepsy, utilization pattern and Compare safety profiles of antiepileptic, drug compliance and drug related problems in the selected epileptic patient population thereby counseling the

patients and creating the awareness about the reactions of anti-epileptic drugs and its positive effect on their quality-of-life better seizure control and decreasing the hospitalization, morbidity and mortality [10]. The classification of Antiepileptic drug for the treatment of epilepsy. Any unexpected or unwanted reactions cause by the administration of drugs.



Myoclonic seizure



Tonic – Clonic Seizure



Tonic Seizure



Atonic Seizure

The detection and preventions of ADRs are very important as they can cause not only morbidity but also mortality, so for better patient care reporting of ADRs is necessary [14]. As therapeutic index of antiepileptic drug is narrow and their adverse effect can affect any organ of the body and

30% of people discontinue due to intolerance According to the study it is shown that some of the AED had shown some severe neurological reactions, idiosyncratic effects and some chronic effects like hyperplasia [15].

CLASSIFICATION OF ANTI-EPILEPTIC DRUGS

1. **Hydantoin derivatives:** Phenytoin, Fosphenytoin
2. **Barbiturates:** Phenobarbitone and Primidone
3. **Iminostilbenes:** Carbamazepine , Oxcarbazepine
4. **Succinimide:** Ethosuximide, Methsuximide
5. **GABA-transaminase inhibitors:** Sodium valproate, vigabatrin
6. **GABA reuptake inhibitors:** Tiagabin
7. **GABA agonists:** Gabapentin
8. **Benzodiazepines:** Clonazepam, Diazepam, Clobazepam, Lorazepam
9. **Miscellaneous:** Lamotrigine, Sulthiame, Phenacemide and amphetamine.

This study plays a key role in serving achieved health care system understand, interpret, evaluate and improve the prescribing, administration and use of medications [16]. It's involved a comprehensive review of epileptic patient's medication and health history before, during and after dispensing in order to attain appropriate therapeutic decision making and positive epileptic patients outcomes by this study determined to prevent the use of pointless or inappropriate drug therapy, prevent drug related problems and improve overall effectiveness.

There were some criteria that were used to select articles for the study literature review which was based on the study questions or study theme. Commonly based on inclusion criteria and exclusion criteria and those literatures review selected which was observationally design and by population characteristics or based on Adverse drug

reactions of Antiepileptic Drug, indicated the scope and purpose of the literature. Relevant tools to collect data were developed based on systematic literature review on drugs reactions in epileptic patient from a observational study that was conducted. Database Embase, Medline, PubMed, Elsevier and many more were searched for original research on Adverse Drug Reactions in epileptic patients. Search terms used were severe or adverse reactions or pharmacovigilance of antiepileptic drug or anticonvulsant, Google scholar and manual reference searches were also carried out¹⁹. A requirement trial to evaluating the number of participants who could potentially involve in the study and then define inclusion and exclusion criteria was completed in epilepsy populaces. All the data pertaining to the study were collected and recorded in a specially designed data collection form [22]. Self-prepared structure questionnaire or data

collection form contain five parts- patients demography, patient's disease details, medication detail, drug related problems. All the variables for the study were evaluated. The collected data were thoroughly screened to check the Safety profiles of different generation of Antiepileptic Drug, Drug compliance and Drug Related Problems [29]. Systematic sampling was done in epilepsy patients after settle on the sample size. Population type (all age group both male and female) conditions. Patients who had known case or suffer from epilepsy and diagnosis (provisional and confirmatory) and with other co-morbid condition, prescribed antiepileptic drugs considered for analysis [41]. Patient not willing to giving answer, pregnant women or lactating women who are on antiepileptic drug are exclude from the study. Data were collected in a well-designed form.

MATERIALS AND METHODS

Research methodology is the systematic way to solve the research problem. It includes the step that researcher adopt to study his problem with the logic behind. It indicates the general pattern of organizing the procedure of gathering valid and reliable data for an investigation. This chapter provides a brief description of the method adopted by the investigator to conduct this study. This

chapter deals with research approach; study design, the sample and sampling technique. It further deals with the development and description of the tool, pilot study, data collection, procedure and plan of analysis. The study of six months duration was performed in the multispecialty healthcare setting and is distributed into three phases. All the relevant and necessary data was collected from the following sources-patients consent form, Patients data collection form, Patient record file/prescription Treatment chart. Patient interview, Laboratory reports. Also, Data was achieved from every patient at the initial and consequent out patient's visits, also from past medical records as well as family members. The study was led on a patient pool of 92 people. This study was conducted for a period of 6month. Prospective observational study. This study was conducted in both in and outpatient setting of the neurology department at Teerthanker Mahaveer Hospital, Moradabad, Uttar Pradesh. It is a near out 800 bedded multispecialty tertiary care teaching hospital. Patients were included in the study if, Patients suffering from epilepsy from any cause. Both the genders with all age groups. Willing to sign informed consent included the study. Patients were excluded in the study if patients who do not fulfill inclusion

criteria, patients with incomplete information, pregnant and breast-feeding women.

STUDY PROCEDURE

In this prospective study spanning six months collect with the main objective of drug utilization review in epileptic patients and analyzed the prescription data of patient who met the study criteria were enrolled in the study for assessing Drug Utilization after obtaining the written consent from patient/patient care taker in medical units and neurology units. Data were collected from case sheets of both in-patients and out-patients attending the clinic for follow-up. A suitably designed data collection form was used to record all the necessary data including patient demographic details, known or newly diagnosed epileptic patients, Type of risk factor of epileptic seizure, antiepileptic drug data, drug -related problems like adverse drug reaction, drug–drug interaction, sub-therapeutic or overdose, untreated condition, medication error, drug compliance, drug compliance level was measured and thereby identifying the factors affecting drug compliance which reported by patients were recorded. The data collected to a detailed structured questionnaires, all patients of both gender between infants to 80 years and were on antiepileptic drugs were

included in the study and was coded, entered in the excel sheet and analyzed by descriptive statistics. The collected data were thoroughly reviewed by academic clinical pharmacist to maintain the quality of data. Transcribed data were also reviewed against data collection Performa to minimize transcription error.

METHOD OF DATA COLLECTION

Patients data such as the type of epilepsy and its risk factors, number of AED prescribed, dose and duration of illness, drug-related problems and drug compliance if any during the therapy and whether drug monitoring was carried out or not was collected from various data sources case sheets, out-patient cards, laboratory reports etc. The follow-up was done based on the next appointment given by treating clinician. The follow-up was done for a period of 6 months. The enrolled patients case sheet/prescription letter was reviewed every day or every time during ward round participation or follow-up time. serious/major drug-drug interaction and adverse drug interaction or other drug-related problems were identified by the help of a neurologist and by using standard text books and software like MICROMEDIX , MEDSCAPE software available in the department. The identified drug- related

problems were discussed with the physician for further management.

STATISTICAL METHODS: The data were subjected to descriptive statistical analysis using Microsoft Excel. Microsoft word, the collected data were cleared, categorized and analyzed using Microsoft Excel and the results were presented in excel have been used to generate bar graph, pie chart, histogram, and tables. Frequencies, percentage mean value were obtained and chi-test, Annova, t-test was applied for comparative analysis.

RESULTS

A total of 64 patients were recruited into this study. The median age of the patients was 26.2 years. A total of 47 patients were on polytherapy and 17 on polytherapy. Over half of the patients received either Levetiracetam or carbamazepine as monotherapy. Seventy-four per cent of all AED prescriptions were old generation drugs. The most frequently prescribed drugs were Levetiracetam (42%), carbamazepine (32%), lamotrigine (12%) and Sodium valproate (9%; **Table 1**). In conclusion, polytherapy increases the possibility of ADRs in patients. Physicians should give AED polytherapy only when the maximum therapeutic doses of monotherapy are ineffective. Both clinicians and parents

should monitor AED treated patients for adverse reactions, especially behavioral problems.

A total of 24 ADRs were recorded in 20 of the 64 patients (31%). Twenty-six of the 47 patients (60%) on polytherapy experienced ADRs. In contrast, 17 of the 64 patient (21%) on monotherapy experienced ADRs. The risk of ADRs was significantly lower in patients receiving monotherapy than those in polytherapy. The most common ADRs were behavioural problems and somnolence (**Table 2**). These accounted for approximately one-third of all ADRs. Rash was the third most common ADR, and was most common with carbamazepine and lamotrigine. AEDs were discontinued in 23 children (**Table 1**). Dose was reduced in 20 patients. Approximately one in 10 patients receiving valproic acid, carbamazepine and lamotrigine had to stop treatment due to toxicity. Behavioral problems were the most frequent reason cited for valproic acid, and rash for both carbamazepine and lamotrigine. All three children receiving phenytoin had to stop treatment for a variety of ADRs. All but four ADRs were considered either probable or possible by both the Naranjo algorithm and the paediatric clinical pharmacologist. The majority were considered probable Naranjo. Most ADRs were moderate (71%)

with two severe. The three severe ADRs were Steven Johnson syndrome (1) and respiratory arrest (1).

DISCUSSION

About one-third of patients receiving AEDs in this study developed at least one ADR during treatment. Carbamazepine, valproic acid and lamotrigine were the most frequently prescribed AEDs. A similar AED prevalence pattern has been reported in other studies. These were also the most common causes of ADRs. The risk of treatment discontinuation was one in twelve patients for these three AEDs, with rash being the most common cause for carbamazepine and lamotrigine discontinuation. Others have shown similar discontinuation rates due to toxicity in children from carbamazepine and valproic acid; and carbamazepine and phenobarbital. Most AEDs are similar in efficacy but differ in safety [23-24]. A large Chinese study had reported that similar proportions of children on carbamazepine [30], topiramate and valproic acid had adequate seizure control, while significantly more carbamazepine-treated children had treatment discontinuation due to ADRs,

mainly rash. Carbamazepine is therefore not recommended as first-line treatment in Han Chinese without genotyping. Most children in this study received monotherapy [36], with only 25% receiving polytherapy [29]. Monotherapy for epilepsy became standard management in the 1970s as it was recognized that polytherapy was more likely to be associated with drug toxicity. AED used as monotherapy is effective in 60–70% of patients. Additional drugs in refractory patients have been shown to be only marginally beneficial. Polytherapy is associated with a greater risk of drug toxicity in pediatric patients in general, especially those receiving AEDs. More patients receiving polytherapy in this study developed ADRs, with up to a threefold higher incidence of ADR [3].

MARS or Medication adherence rating scale is a scale to measure the patient's compliance with the therapy. It consists of 10 questions which require yes/no responses. The majority of patients (93.54%) had shown compliance with the treatment protocol. Only 6.46% patients were non-complaint with the treatment protocol.

Table 1: Number (%) of patients receiving different AED regime

Drug	Monotherapy (%)	Polytherapy (%)	Total (%)
Levetiracetam	39 (28)	23 (14)	62 (42)
Carbamazepine	36 (26)	08 (4)	44 (31)
Lamotrigine	15 (10)	10 (07)	25 (12)
Sodium valproate	02 (01)	11 (08)	13 (09)
Clobazam	0	12 (9)	12 (08)
Phenobarbitone	04 (03)	13 (10)	17 (07)
Topiramate	02 (02)	04 (04)	06 (07)
Ethosuximide	04 (03)	7 (02)	11 (03)
Phenytoin	0	1 (0.5)	01 (0.5)
Oxcarbazepine	0	1 (0.5)	02 (0.5)
Gabapentin	0	1 (0.5)	01 (0.5)
Clonazepam	0	1 (0.5)	01 (0.5)

Age wise distribution of the patients

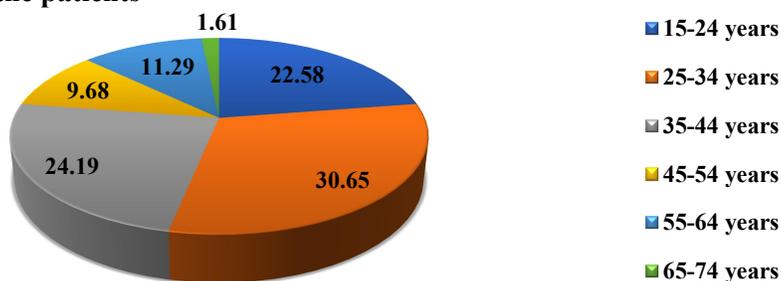


Figure 1: Pie chart showing Age distribution of Patients

Table 2: Adverse reactions to antiepileptic drugs

ADR	VPA	CBZ	LTG	OTHERS	TOTAL
Psychiatry					10
Behavioral problems	2	3	-	TPM (1), PHT (1), LEV (1)	
Depression	1	1	-	(1)	
Anxiety	-	-	1		
Skin and appendage					2
Rash	-	1	-	-	
Steven-Johnson syndrome	-	-	-		
Hair loss	1	-	-		
Metabolic					3
Increased appetite	-	-	-	-	
Reduced appetite	1	-	-		
Weight gain	1	1	-		
Polydipsia	-	-	-		
Nervous system					7
sleep disorders	1	-	1	CLB (1), ETX (1), PBT (1), PHT (1), LEV (1)	
Headache	-	-	-		
Fatigue	-	-	-		
Dizziness	1	-	-		
Blurred vision	-	-	-		
Poor concentration	-	-	-		
Auditory hallucination	1	-	-		
Tremor	-	-	-		
Dystonia	1	-	1		
Increased/new seizure					

Others					3
Fever	-	1	-	ETX (1)	
Enuresis	-	-	-		
Incontinence	-	-	-		
Renal stone	-	-	-		
Respiratory arrest	-	-	-		
Paraldehyde Thrombocytopenia	-	-	-		
Elevated ALT	1	-	-		
Gum hypertrophy	-	-	-		
TOTAL	11	6	3	4	24

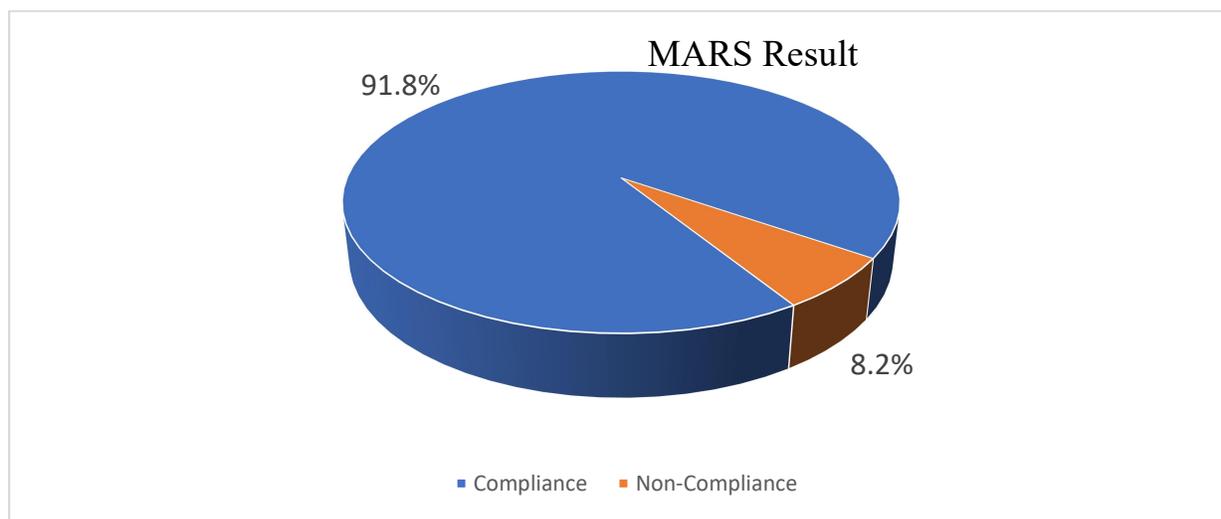


Figure 2: Pie chart showing Medication adherence rating scale (MARS) result

ACKNOWLEDGEMENT

This project marks the end of our journey in academic fraction of obtaining the degree of Doctor of Pharmacy. Carrying out this task had been neither easy nor ephemeral. No good work can be done bereft of helping hands. Primarily, we would like to thank our parents, for their immense love, care, guidance, support, patience, motivation and countless sacrifices, which have given us the strength to endure all toil and turmoil in life. We owe everything to them. Their vision was

what provoked us to give our best in everything and kept pushing us up whenever we took a dig at the ground. We would love to extend our gratitude to our siblings who is always there to make us smile whenever we felt gloomy. and gave us an energy boost while overlooking our ignorant attitude.

At this moment of accomplishment, first of all we would like to be grateful to our institutional guide, **Mrs. Sarita Jangra Bhyan**, Assistant Professor, Department of Pharmacy Practice, TMCOP. Under her

guidance we successfully overcame many difficulties and learned a lot. Some debts can never be re-paid and one has to remain obliged until their last day.

We find ourself with paucity of words to express our most sincere gratitude and thankfulness to our clinical guide, **Dr. Rajendra Pandey**, Professor & Head Department of Neurology, TMMC & RC, who always stood as a guiding beacon. This will be an asset to us which we will relish all our life that we have worked under such pinnacle of Neurology.

The person, who opened the doors for us to enter into Doctor of Pharmacy and welcomed us with warmth to become a part of the TMCOP family, deserves our biggest and most extreme gratitude. **Prof. Anurag Verma**, Director TMCOP, without who's able and streamline guidance, constant and vigilant supervision, constructive and fatherly criticism, and immutable encouragement, this imposing work would not have seen light of the day. Our mentor **Mrs. Sarita Jangra** and respected faculty members who have always guided us since our early days. All of these valued faculties have always been keen to resolve our queries and persuade our curiosity in every field apart from their proficiency. Our friends, Whole Pharm.D. 2015 Batch, especially

hostler boys, also deserves a right to be acknowledged for their consistent support and understanding. Besides this, we are obliged to all those people who have knowingly or unknowingly helped us in the successful completion of this project.

Gracious, Pankaj Singh Negi, Shubham Gangawat, Paluck, Indradeep Yadav.

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