

Monitoring of Adverse Drug Reactions in Commonly Used Anti-Epileptic Drugs

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ABSTRACT: Background: It is of concern that epilepsy is often suboptimally managed, especially in developing countries. The aim of the present study was to evaluate the prescription pattern & Adverse Drug Reaction (ADR) profile of Antiepileptic drugs (AEDs) therapy in the hospital visiting patients, come from different geographical regions with a fair representation of both urban and rural populations.

Methods and Materials: This observational study was carried out among a sample of epilepsy patients attending the OPD of a tertiary care hospital. All the adverse events reported spontaneously as well as founded by researcher during the interview at each visit were recorded in the case record form with all necessary information.

Results: A total of 306 epileptic patients were monitored, 54.2% were male and 45.8% were females. Majority of the study population were adults. Majority of the epileptic patients were affected with generalized seizure (60.50%). Phenobarbital (34.6%) was the most prescribed drug in monotherapy followed closely by Carbamazepine (33.3%). The present study shows that Carbamazepine is not associated with the ADRs. The patients who have taken drug Carbamazepine are less likely to get ADRs of moderate and severe type. This indicates the negative relationship of ADR with Carbamazepine.

Conclusion: Appropriate AED selection and careful evaluation of drug adverse effects play a crucial role in achieving the ultimate target goals of seizure freedom from epilepsy.

KEYWORDS: Epilepsy; Adverse Drug Reaction, Antiepileptic Drugs

I. INTRODUCTION

Epilepsy describes a condition in which a person has recurrent seizures due to a chronic, underlying process. It refers to a clinical phenomenon rather than a single disease unit, since

there are numerous forms and causes of epilepsy.¹ Epilepsy is a common neurological disorder which demands immediate medical attention and often long-term therapy.

Epilepsy is a common neurological condition affecting 0.5-1% population. Epidemiological studies of epilepsy all over the world have shown higher prevalence rate for developing countries. Cumulative lifetime incidence of epilepsy in children is 3%.^{2,3}

Most patients with epilepsy depend on medical treatment with antiepileptic drugs (AEDs) to achieve control of their seizures. The overall aim in the treatment of epilepsy should be complete control of seizures and no adverse reaction due to medication with an optimal quality of life.⁴

Commonly used AEDs for epilepsy are carbamazepine (CBZ), phenytoin (PHT) and phenobarbitone (PB).⁵ These drugs due to their complex pharmacological properties and narrow therapeutic index lead to various adverse drug reactions (ADRs) which often dictate the choice of AEDs and subsequent adjustment of therapy.⁶

In a meta-analysis by fatal ADRs were ranked as fourth to sixth leading cause of death among both adults and children in United States.⁷ Meta-analysis of 17 prospective studies conducted in the US and Europe showed incidence of ADRs among hospitalized children to be 9.5% with severe reactions accounting for 12% of the total.⁸ One study reported that AEDs were responsible for 11% of overall ADRs. In another study on assessment, monitoring and reporting of ADRs in an Indian hospital, AEDs were responsible for 5% of ADRs among all of the prescribed drugs.⁹

AEDs differ in the type and severity of adverse effects, mostly during initiation and early treatment. The ability of patients to tolerate initiation of AED can be a function of several factors, including how rapidly a dose is escalated, the length of time needed to develop tolerance to

early toxicity and the rate at which blood levels of a drug increase, as well as complexity of the titration schedule.¹⁰ For some AEDs, initiation with a small dose given at bedtime, followed by slowly increasing the dose, or dividing a total daily dose into multiple small portions taken throughout the day, and may allow a patient to develop tolerance but increases the complexity of the regimen. Patients will often adapt to a regimen over a period.¹¹

II. METHODS

A cross sectional survey based observational study was conducted at Department of Medicine of tertiary healthcare. Patients visiting Department of General Medicine (Neurology) of tertiary care teaching hospital, were screened for the study and subjects who satisfy the inclusion and exclusion criteria mentioned below were recruited for the study.

Inclusion Criteria

- Patients with confirmed diagnosis of epilepsy who is on treatment for at least 1 year.
- Age group between 15 years to 50 years.
- Patients who have consented to participate.
- Patients who were on single anti-epileptic drug

III. RESULTS

The BMI of the study group was analyzed and

during the study period.

- Patients who are taking Phenobarbital in 60-120mg or Carbamazepine in 400-1200mg or Phenytoin in 200-400 mg dose range per day during the study period.

Exclusion Criteria

- Patients with known significant disability- mental retardation, motor, visual, hearing or speech impairment
- Patients not willing to comply with the study procedure.
- Patients who are on two or more anti-epileptic drugs during the study period.
- Patients who are not taking Phenobarbital in 60-120mg or Carbamazepine in 400-1200mg or Phenytoin in 200-400 mg dose range per day during the study period.

Data analyses

ADRs identified with each drug were recorded using computer software and categorized and analyzed individually with the drug. Socio demographic data, life style, history, family history etc. were also recorded based on a structured questionnaire and the data was also statistically analyzed.

shown in Table No 1 and Figure No 1. It shows that 248 were with normal BMI, 23 were obese, 31 mild malnutrition and 4 moderately malnourished.

BMI	Number	%	% ADRs			
			No ADR	Mild	Moderate	Severe
Normal (19.0-24.9)	248	81	85.08	6.85	7.26	0.81
Mild Malnutrition (7.0-18.9)	31	10.1	83.87	8.57	8.57	-
Moderate Malnutrition (16.0-16.9)	4	1.3	75.00	-	-	-
Severe Malnutrition (<16.0)	-	-	-	-	-	-
Obese (25.0)	23	7.5	95.65	4.35	-	-

Table No 1. BMI distribution of the study group

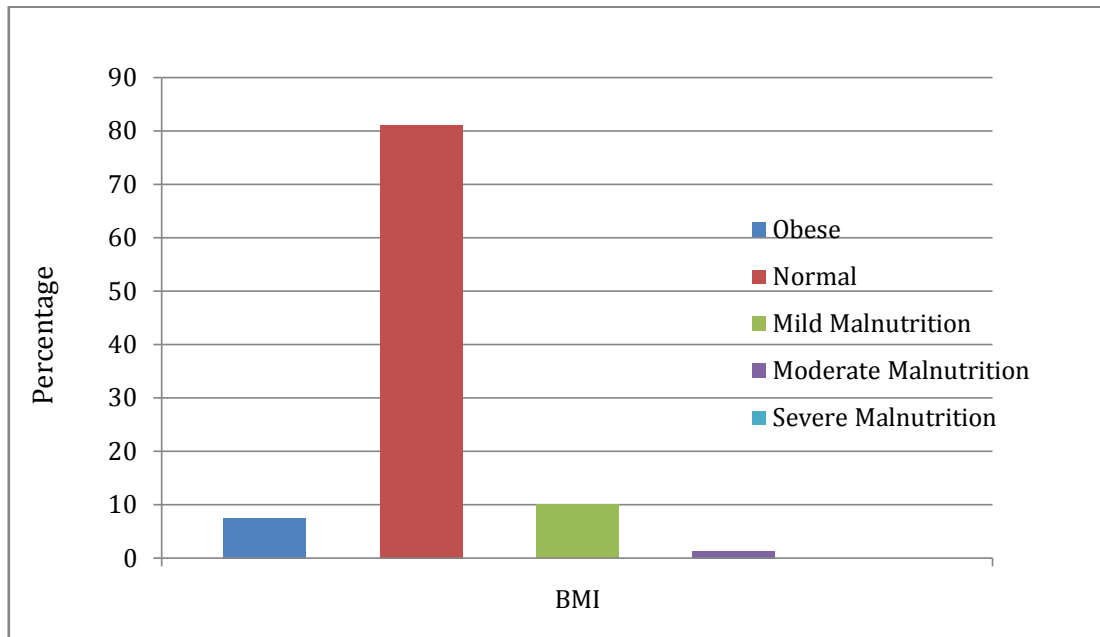


Figure No. 1. Body Mass Index of the study group

The education level of the study group of PWE was also statistically analyzed, and it had both illiterates (4) and literates (302). Most of the persons were reasonably well-educated as shown in Table No 2 & Fig. No. 2.

Education	Number	%	% ADRs			
			No ADR	Mild	Moderate	Severe
Illiterate	4	1.3	100	-	-	-
literate	302	98.7	85.43	6.95	6.95	0.66

Table No. 2. Education level of the study group

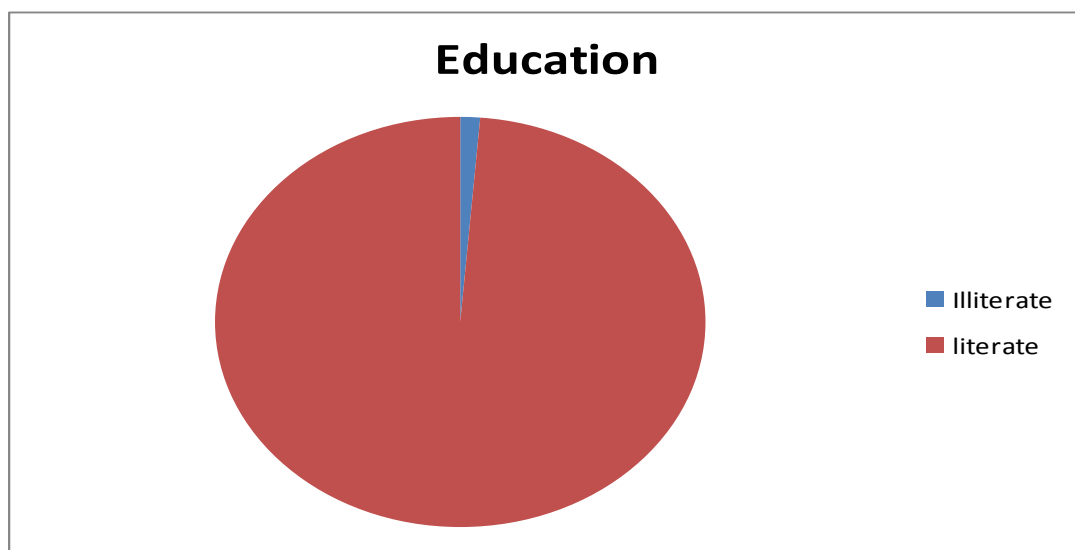


Figure No. 2. Education level of the study group

The study group was almost equally distributed in the use of the drug under study, 34.6% used Phenobarbital, 32.0% used Phenytoin and the remaining 33.3% were on Carbamazepine (Table No 3, Fig No. 3).

Drugs	Number	%	% ADRs			
			No ADR	Mild	Moderate	Severe
Drug Phenobarbital (PB)	106	34.6	84.91	10.38	4.72	-
Drug Carbamazepine (CBZ)	102	33.3	89.22	6.86	3.92	-
Drug- Phenytoin (PHT)	98	32	82.65	3.06	12.24	2.04

Table No 3. AED used by the study group

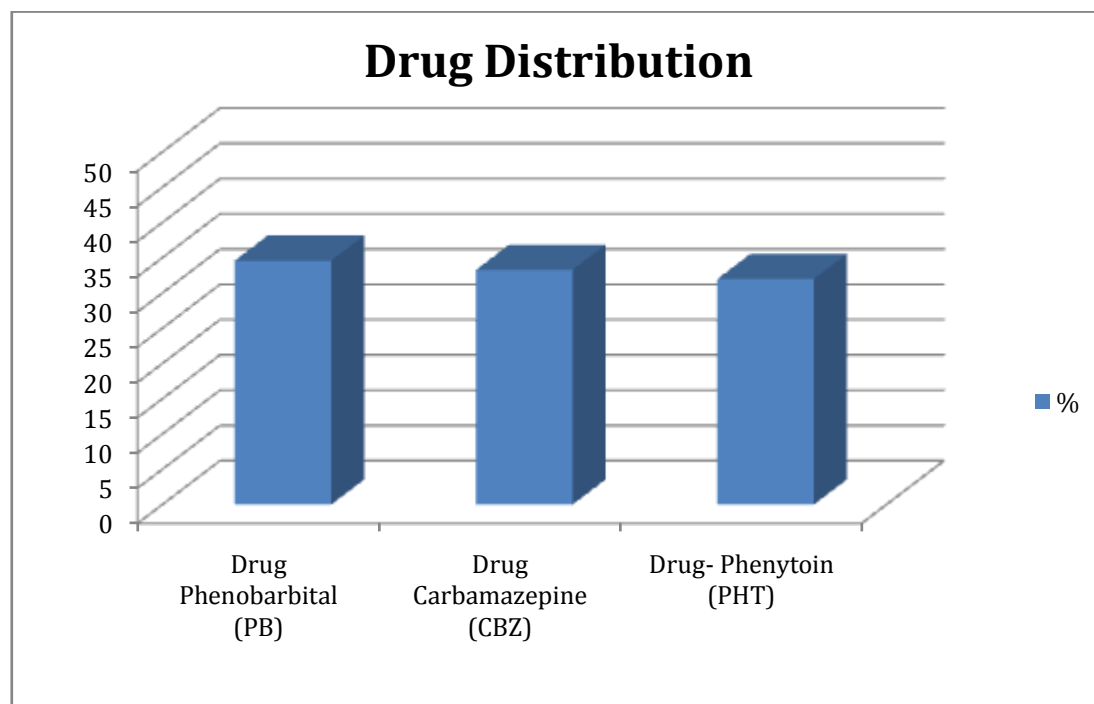


Figure No. 3. Drug used by the study group

One hundred and eighty five patients (60.50%) had generalized type of seizures while 121 (67 + 54) had partial seizures, taking simple and complex types together (Table No 4 and Figure No 4).

Type of seizures	Number	%
SPS (Simple Partial Seizure)	67	21.90
CPS (Complex Partial Seizure)	54	17.60

Table No 4. Epileptic seizures of the study group

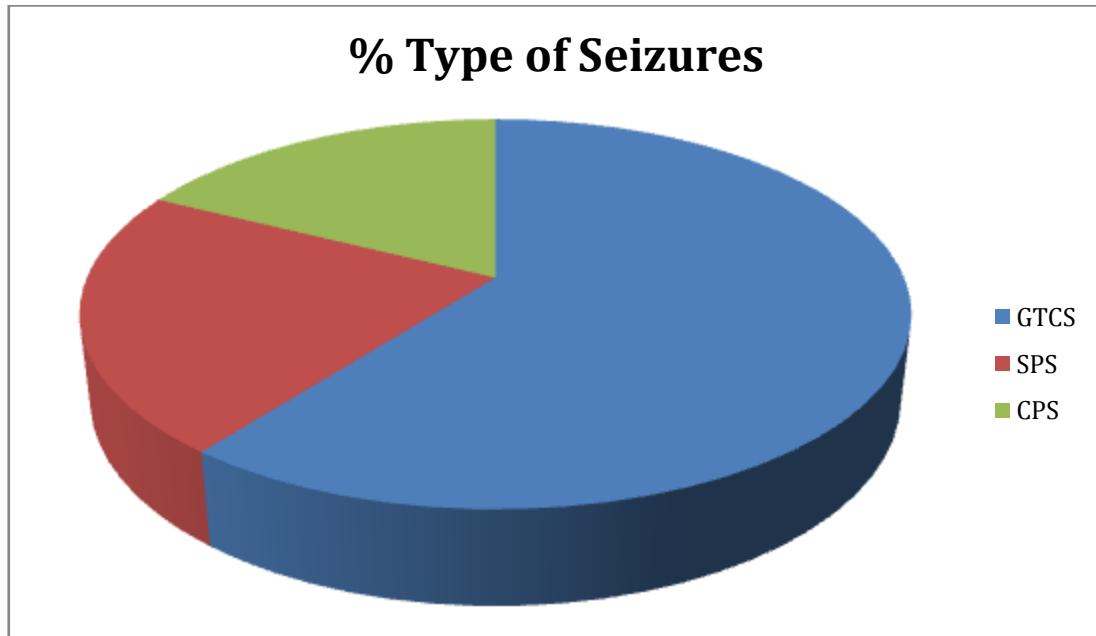


Figure No 4. Epileptic seizures of the study group

Among the patients taking Phenobarbital (n=106), 16 developed ADRs of mild and or moderate nature. No severe or lethal type of ADRs occurred. Eleven had only minor type of ADRs and 5 moderate type of ADR. Figure No 5 shows the incidence of ADRs with Phenobarbital.

ADR	Phenobarbital- PB	
	Given (n=106)	Not-Given (n=200)
No ADR	90 (84.91)	172 (86)
Mild ADR	11 (10.38)	10 (5)
Mod ADR	5 (4.72)	16 (8)
Severe ADR	-	2 (1)

Table No 5. Association of ADR with drug PB

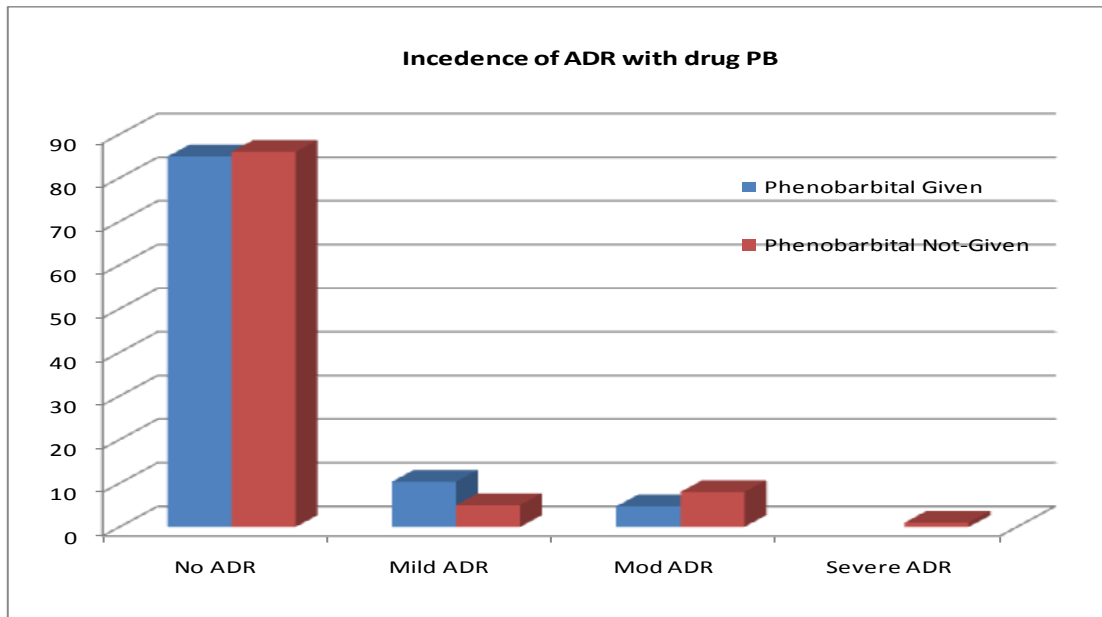


Figure No 5. Incidence of ADR with drug PB

In the case of Carbamazepine (n=102), 11 patients developed ADRs (mild or moderate). No case of severe or lethal type of ADR was found. Out of the 11 cases of ADRs, 7 were mild and 4 moderate. Figure No 6 give the details of the association of ADR with Carbamazepine.

ADR	Carbamazepine CBZ	
	Given (n=102)	Not-Given (n=204)
No ADR	91 (89.22)	171 (83.82)
Mild ADR	7 (6.86)	14 (6.86)
Mod ADR	4 (3.92)	17 (8.33)
Severe ADR	-	2 (0.98)

Table No. 6. Association of ADR with drug CBZ

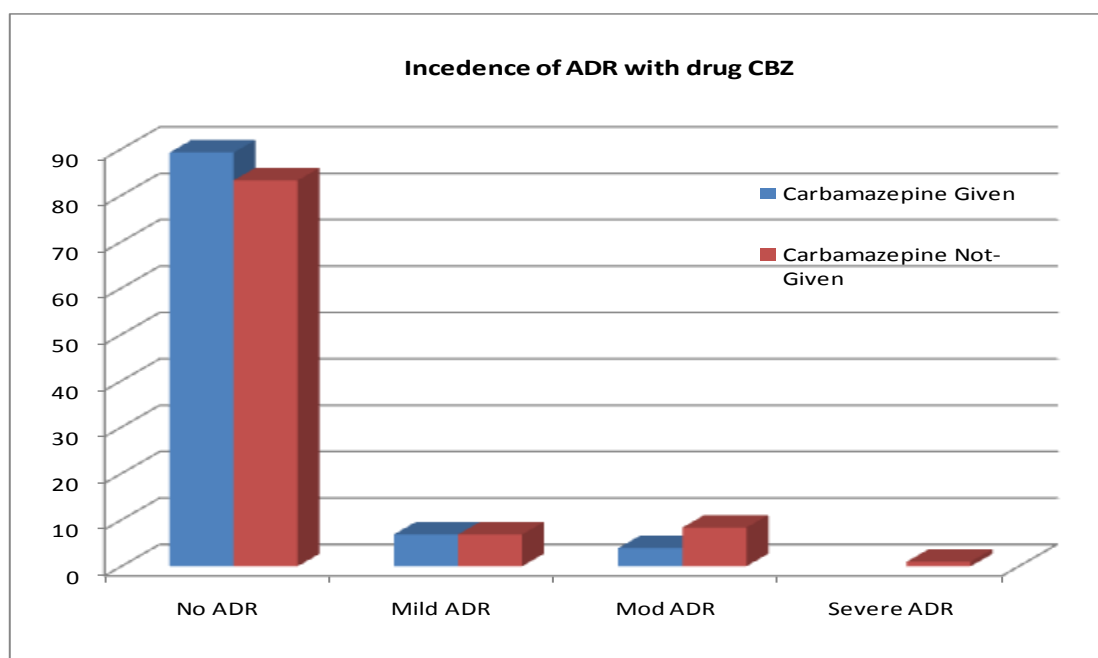


Figure No 6. Incidence of ADR with drug CBZ

In the case of Phenytoin (n=98), 17 developed ADRs. Though no case of lethal type of ADR was reported, two cases of severe ADRs and

12 cases of moderate ADR were found. Three cases were of mild type. The details of association of ADRs with Phenytoin are shown in Figure No 7.

ADR	Phenytoin PHT	
	Given (n=98)	Not-Given (n=208)
No ADR	81 (82.65)	181 (87.02)
Mild ADR	3 (3.06)	18 (8.65)
Mod ADR	12 (12.24)	9 (4.33)
Severe ADR	2 (2.04)	-

Table No 7. Association of ADR with drug PHT

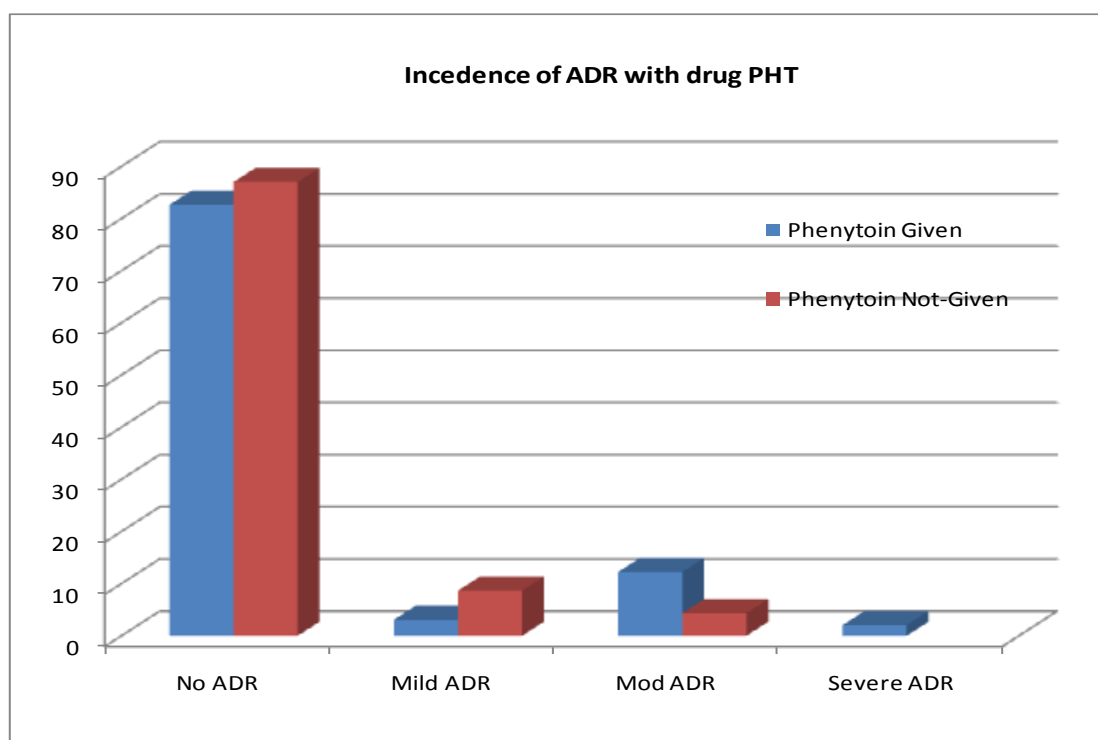


Figure No 7. Incidence of ADR with drug PHT

DISCUSSION

In this study no statistically significant association was found between the BMI and the occurrence of ADRs in PWE (Table No 1).

It is observed in the study that epileptic persons are mostly suffering from GTCS type of epilepsy as compared to others (Table No. 4).

One of the reasons for not considering Phenobarbital as a drug of first line choice for treating epilepsy is its reported frequency of ADRs. In this study the analysis given in Figure No 5, 6 and 7 shows that Phenobarbital is associated with mild ADRs. It shows that patients taking the drug are more likely to get mild ADR. In the case of moderate and severe ADRs, the patients who had taken the drug are less likely to get the ADR.

It was also reported that up to one third of the patients using Carbamazepine can have ADR of any type. However the present study shows that Carbamazepine is not associated with the ADRs. The patients who have taken drug Carbamazepine are less likely to get ADRs of moderate and severe type. This indicates the negative relationship of ADR with Carbamazepine.

Phenytoin which is considered as a standard anti-epileptic drug and against which all other drugs are measured has been found to cause heavy incidence

IV.

of ADRs extending up to 50% of the users. In this study, Phenytoin is found positively associated with moderate ADR. Table No 7 (association of ADR with drug Phenytoin) indicates that the PWE using Phenytoin were more likely to get moderate ADRs.

V.CONCLUSION

The study shows that ADR is not a major or serious issue in the case of anti-epileptic drugs, Phenobarbital and Carbamazepine. In the case of Phenytoin, the findings indicate that the drug's use should be supported with facilities for therapeutic monitoring of drug concentration in body fluids. Hence it is recommended that therapeutic drug monitoring (TDM) facilities have to be initiated in all major hospitals where epileptic patients are provided expert medical care.

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