

## Complications of Antiepileptic Drugs in Hospitalized Patients in Shahid Motahari Hospital of Urmia from 2010 till the end of 2016

Ezatolah Abbasi<sup>1</sup>, Ahad Ghazavi<sup>2\*</sup>, Mohammad Valizadeh<sup>3</sup>, Mustafa Farshi<sup>4</sup>, Mohammad Radvar<sup>5</sup>

Received 27 February, 2020, Accepted for publication 23 June, 2020

### Abstract

**Background & Aims:** Seizure is a common neurological disease with many therapies, especially antiepileptic drugs being used to treat it. Any adverse effects caused by taking antiepileptic drugs are called antiepileptic side effects. The purpose of this study was to evaluate the side effects of antiepileptic drugs in patients admitted to Shahid Motahari Hospital of Urmia from 2010 until the end of 2016.

**Materials & Methods:** This descriptive study was conducted after the approval of the Ethics Committee of Urmia University of Medical Sciences. In this study, 100 epileptic children with complications of antiepileptic drugs admitted to Motahari Pediatric Hospital of Urmia from 2010 to 2016 were studied. The sampling method was census using the keyword drug reaction in patient files. The information was collected through a checklist, which was completed by the project manager based on the information in the patient's file. The checklist consisted of 3 sections. The first part included demographic information of patients including age and sex; the second part included targeted information including the number of seizures, type of anticonvulsant drug used; and the third part included targeted information including drug side effects in these patients.

**Results:** The mean weight SD of the studied patients was 40.09 /1 1.94 kg with a median of 41.50 kg. Most of the adverse events observed in the studied patients were related to skin complications with the frequency of 52 patients (52%). The most common adverse events observed were within the age range of 9 to 10 years with a frequency of 16 patients (16%). Also, there was no significant relationship between the side effects of epileptic drugs and the age of the patients ( $p = 0.844$ ).

**Conclusion:** The renal side effects of antiepileptic drugs in males were higher than females, and the skin and liver complications were higher in females, and the most common side effects were observed within the age range of 9 to 10 years. It also has a direct relationship with the duration of drug side effects. Compared to sodium valproate, Phenobarbital has more side effects in children.

**Keywords:** Seizure, Skin Complications, Anticonvulsants, Drug Side Effects, Liver Disorders

**Address:** Urmia University of Medical Sciences, Urmia, Iran

**Tel:** +984432234897

**Email:** Ghazavi.Ahad@gmail.com

<sup>1</sup> Assistant Professor of Pediatric Neurology, Urmia University of Medical Sciences, Urmia, Iran

<sup>2</sup> Associate Professor of Pediatric Neurology, Urmia University of Medical Sciences, Urmia, Iran (Corresponding Author)

<sup>3</sup> Pediatrician, Urmia University of Medical Sciences, Urmia, Iran

<sup>4</sup> Medical student, Urmia University of Medical Sciences, Urmia, Iran

<sup>5</sup> Assistant Professor of Pediatric cardiology, Urmia University of Medical Sciences, Urmia, Iran

## Introduction

Seizure is a common neurological disease with different therapies including antiepileptic drugs (1). Any adverse effects occurring after taking antiepileptic drugs are called antiepileptic side effects (2). Drug side effects occur in about 1% of children. The most common side effects in children are related to antiepileptic drugs. The most common side effects of antiepileptic drugs are skin reactions such as urticaria and other skin rashes (3). Skin rashes range from maculopapular skin rashes to more serious conditions like toxic epidermal necrosis, DRESS (mnemonic for drug reactions + eosinophilia + systemic symptoms) and Stevens Johnson syndrome characterized with widespread skin eruption and involvement of two or more mucosal membranes (3). Vomiting, diarrhea, fatigue, behavioral changes, dizziness, stomach upset, liver impairment, weight gain, hand tremor, and osteoporosis are other complications of antiepileptic drugs (1).

Among the antiepileptic drugs, phenobarbital, phenytoin, carbamazepine, and lamotrigine carry the highest risk of drug side effects. The previous history of drug sensitivity, co-administration of multiple antiepileptic drugs, drug interactions, and immunodeficiency disease are associated with an increased incidence of antiepileptic drug side effects (1). The most common complications of short-term use include fatigue, dizziness, vomiting, behavioral changes (youth depression, irritability in children), and gastric distress; most commonly caused when taking different anti-epileptic drugs with similar side effects. And tremors that can cause hands or any other parts of body to tremble. (4, 5).

Weight gain is observed in 30% to 50% of patients taking these drugs and is more common in adult females. The average weight gain in adults is 8 kg but can occur in any person and can also lead to hair loss of 0 to 8% of patients treated with these drugs. The hair grows on the

back after discontinuation of the drug, with different combinations (for example curly hair instead of straight hair) (6, 7).

Since other therapeutic properties have been proven for this group of drugs, there are now a wide variety of neurological, psychiatric, and other uses (8). Given the increasing use of these drugs in the community, it is advisable to consider their side effects, especially their deadly skin reactions and given the pivotal role of drug side effects in choosing a suitable drug for better patient compliance and their quality of life in epileptic patients; the need for this study and similar studies is becoming more clear especially with newer drugs with unknown side effects being introduced to the drug market every day (9). The purpose of this study is to gain a general understanding of the risk factors associated with adverse drug reactions to antiepileptic drugs that helps us to choose the right drug and gain better control of seizures.

## Materials and Methods

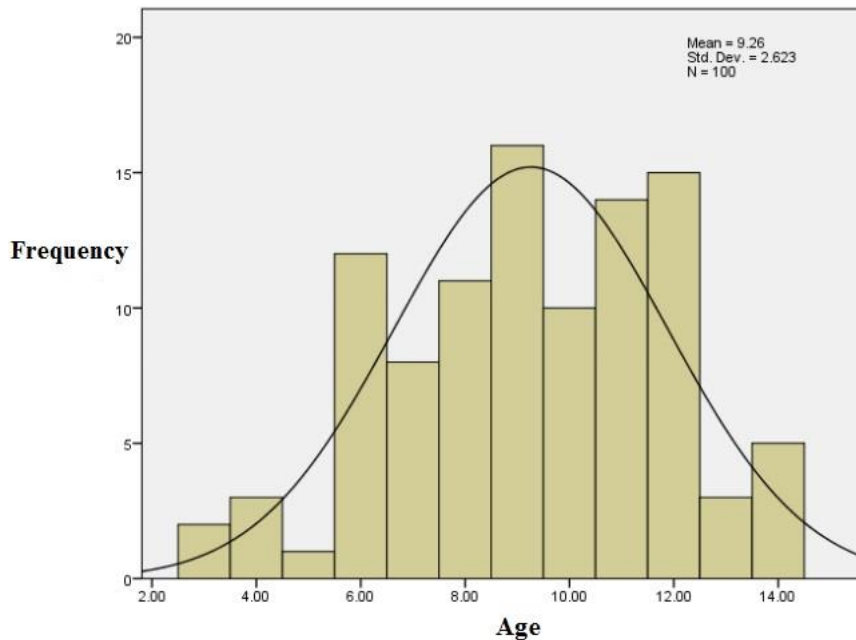
This is a descriptive study. In this study, 100 epileptic children admitted to Motahhari Hospital of Urmia from 2010 to 2016 who experienced complications of antiepileptic drugs were studied. The sampling method was census using the keyword drug reaction in patient records. This study was conducted after getting approval from Ethics Committee of Urmia University of Medical Sciences. The information was collected through a checklist, which was completed by the project manager based on the information in the patient's file. The checklist consisted of 3 sections. The first part consisted of demographic information of patients including age and sex; the second part included information regarding the number of seizures, type of anticonvulsant drug used; and the third part included information about drug side effects in these patients. Those included in this study were epileptic children under 14 years old with definite diagnosis of seizure

taking AED, lacking any specific illness history including ADHD. The patient's personal information was protected and the confidentiality of patients at all stages of research was considered. Data were analyzed by descriptive statistic methods (mean, standard deviation, frequency, percent, and median) using SPSS version 24 statistical software.

## Results

In this cross-sectional descriptive study, 100 children with seizures were studied. The mean weight of

the patients $\pm$  SD was  $40.09 \pm 1.94$  kg with a median of 41.50 kg. The lowest weight was 19 and the highest weight was 46 kg. The mean age of the patients $\pm$ SD was  $9.26 \pm 2.62$  years. The minimum and the maximum age were 3 and 14 years respectively with the mean age of 9 years. The age histogram of patients is shown in Figure 1. Side effects of the antiepileptic drug was evaluated as skin, liver, and kidney complications. The frequency of side effects of antiepileptic drugs by age is shown in Table 1.



**Figure 1:** Age histogram of the studied patients

**Table 1:** Frequency of adverse effects of antiepileptic drugs by age in the patients studied

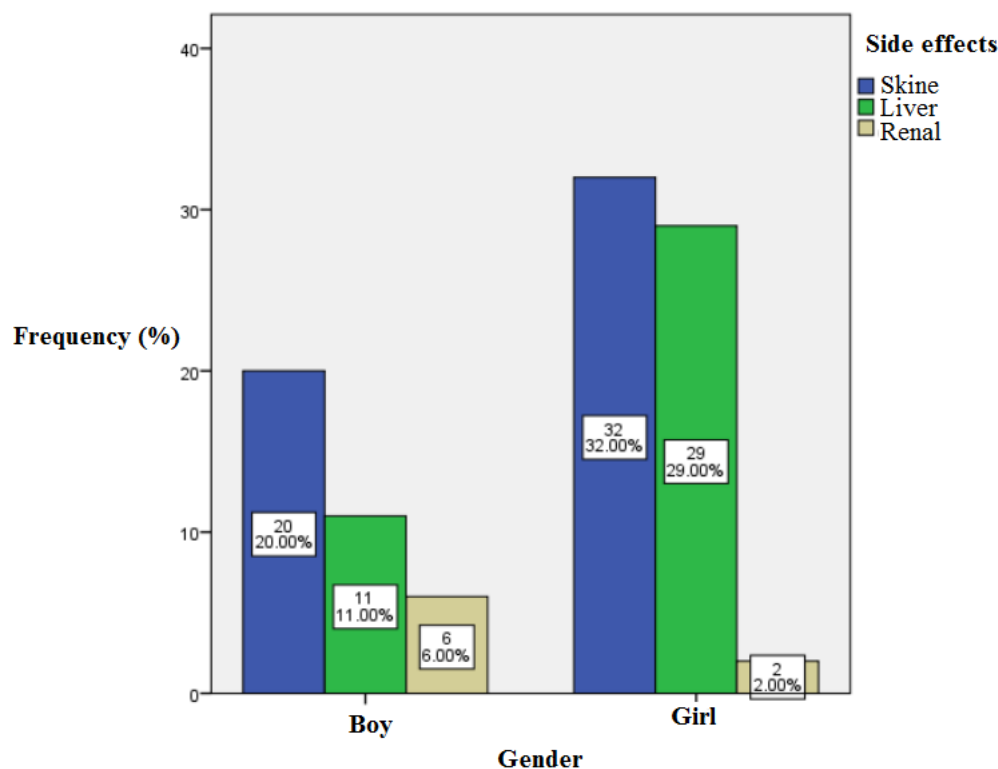
Age range (yr)	Side Effects [Frequency (Percent)]			Total
	Skin	liver	Renal	
3-4	0	0	2(100)	2
4-5	1 (33.3)	2(66.6)	0(0)	3
5-6	1(100)	0(0)	0(0)	1
6-7	5(41.7)	5(41.7)	2(16.7)	12
7-8	3(37.5)	5(62.5)	0(0)	8
8-9	7(63.6)	4(36.4)	0(0)	11
9-10	10(62.5)	5(31.3)	1(6.3)	16
10-11	6(60)	4(40)	0(0)	10

11-12	6(42.9)	7(50)	1(7.1)	14
12-13	7(46.7)	6(40)	2(13.3)	15
13-14	2(66.7)	1(33.3)	0(0)	3
14	(4(80)	1(20)	0(0)	5
Total	52(52)	40(40)	8(8)	100

According to the data from Table 1, the highest rate of adverse events observed in the studied patients was related to skin complications with the frequency of 52 patients (52%). Most age-related adverse events were within the age range of 9 to 10 years with a frequency of 16 patients (16%). Also, there was no significant relationship between the side effects of epileptic drugs and the age of the patients ( $p = 0.844$ ).

Of the 100 patients studied, 37 (37%) were male and 63 (63%) were female. The frequency of side effects of

the antiepileptic drugs studied by sex is shown in Figure 2. According to the obtained data, the most common drug side effect in male sex was related to skin complications with the frequency of 20 patients (20%). In female gender, the common side effects were skin complications with 32 patients (32%) followed by liver complications with 29 patients (29%). Also, there was a statistically significant relationship between drug side effect and sex ( $p = 0.0001$ )



**Figure 2:** Frequency of Epilepsy drug Side Effects by Sex of the Patients

The frequency of adverse effects of antiepileptic drugs according to the duration of drug use in the

patients is shown in Table 2. The highest drug use time was 3 years and the lowest drug use time was 1 year. The

most common adverse event at 3 years was related to 23 patients (63.9%). Also, there was a significant

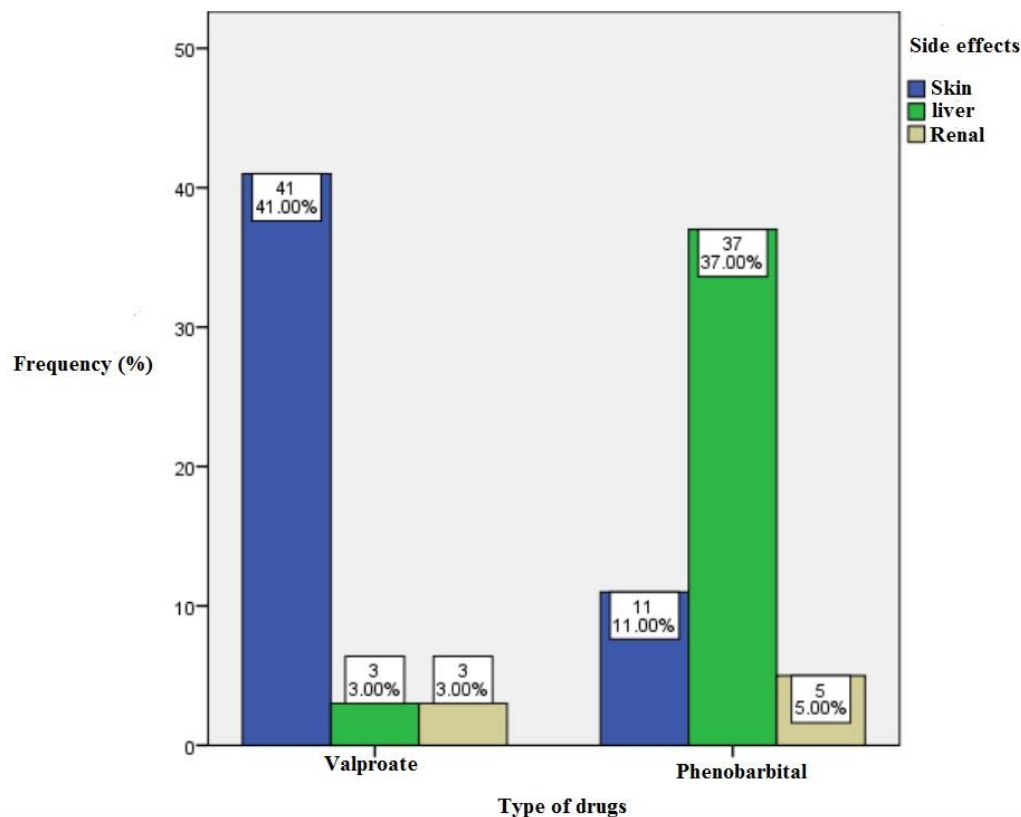
relationship between the duration of therapy and the side effects of antiepileptic drugs ( $p = 0.016$ ).

**Table 2:** Frequency of side effects of Antiepileptic drugs according to the duration of drug use

duration of Drug Use (yr)	Side Effects [Frequency (Percent)]			Total
	Skin	liver	Renal	
1	13(44.8)	16(55.2)	0(0)	29
2	16(45.7)	14(40)	5(14.3)	35
3	23(63.9)	10(27.8)	3(8.3)	36
Total	52(52)	40(40)	8(8)	100

The antiepileptic drugs studied in this study included valproate and phenobarbital. 47 patients (47%) were taking valproate and 53 patients (53%) were taking phenobarbital. The more common adverse events were related to Phenobarbital and its hepatic complications in 37 patients (37%) and skin disorders affecting 11 patients (11%). In contrast, the most common

complication experienced with valproate was skin disorders in 41 patients (41%). Figure 2 shows the frequency of side effects of antiepileptic drugs according to the type of AED. There was a statistically significant relationship between the type of AED and the frequency of adverse events observed ( $p = 0.0001$ ).



**Figure 3:** Frequency of side effects of antiepileptic drugs according to the type of AED

The mean of the standard deviation of ALT, AST, WBC count, differential neutrophil count, and platelet count are shown in Table 3.

**Table 3:** Results of Preclinical Trials Based on Side Effects in Patients under Study

Result	Side Effects [Mean ± SD]		
	Skin	liver	Renal
ALT (IU/L)	15.58±3.84	68.13±9.70	18.30±4.01
AST (IU/L)	14.02±3.12	55.41±8.61	15.07±3.37
WBC (n)	15548.62±7484.29	14241.72±7399.68	14090.47±6690.40
Neutrophil (%)	57.2±18.7	50.1±19.4	45.1±18.7
Platelet (×103)	355.03±146.09	384.93±141.34	410.26±137.53

The frequency of the type of treatment performed in the patients is shown in Table 4; with 58 patients (58%) taking corticosteroid and 42 patients (42%) taking IVIG.

Also, there was no significant relationship between the types of treatments and different adverse events observed (p = 0.29).

**Table 4:** Frequency of the type of treatment in the patients according to the type of adverse event

Treatment	Side Effects [Frequency (%)]			Total
	Skin	liver	Renal	
Corticosteroid	30(51.7)	23(39.7)	5(8.6)	58
IVIG	22(52.4)	17(40.5)	3(7.1)	42
Total	52(52)	40(40)	8(8)	100

**Discussion**

This cross-sectional descriptive study was performed on 100 children with seizures admitted to Shahid Motahari Hospital of Urmia from 2010 to 2016. The mean weight of the patients ± SD was 40.09 ±1 1.94 kg with a median of 41.50 kg. The lowest and highest weight was 19 and 46 kg, respectively. The mean age of the patients was 9.26 ± 2.62 years. The minimum age was 3 years and the maximum age was 14 years. The age histogram of patients is shown in Figure 1. Side effects of the antiepileptic drug were evaluated as skin, liver, and kidney complications. Most of the adverse events observed in the studied patients were related to skin complications with the frequency of 52 patients (52%). Most age-related adverse events were within the age

range of 9 to 10 years with a frequency of 16 patients (16%). Also, there was no significant relationship between the side effects of antiepileptic drugs and the age of the patients (p = 0.844). In a 2008 study by Senacom et al., the incidence of adverse events reported by patients themselves was studied. In this study, unlike ours, there was a significant relationship between the age of patients and the type and frequency of adverse events observed (10).

In our study, out of 100 patients, 37 (37%) were male and 63 (63%) female. According to the obtained data, the most common drug side effect in male sex was related to skin complications with the frequency of 20 patients (20%). In female gender, the common side effects were skin complications in 32 patients (32%) and

liver complications in 29 patients (29%). Also, there was a statistically significant relationship between drug side effects and sex ( $p = 0.0001$ ). It seems that males have a higher rate of renal complications than females due to hormonal changes in growth age and other environmental factors. In a 1988 study by Herranz et al., the side effects of phenobarbital, valproate, phenytoin, carbamazepine, and sodium valproate were studied. Of the 392 patients studied, 189 (48.21%) were male and 203 (51.79%) were female. In their study, renal adverse events were higher in males. Also, there was a significant relationship between patients' gender and drug side effects ( $p = 0.001$ ), which is consistent with our study (11).

In this study, there was a significant relationship between the duration of drug use and side effects of antiepileptic drugs ( $p = 0.016$ ). According to the data, it seems that by increasing the duration of drug use, the rate of chronic drug side effects, especially renal complications, increases. In a 1987 study by Vining et al., the adverse effects of antiepileptic drugs over time were recorded in children. According to the results of this study, there was a significant relationship between increased duration of treatment and drug side effects ( $p = 0.001$ ). Also, the most common drug side effects were skin complications; which is compatible with our findings.

In this study, antiepileptic drugs included valproate and phenobarbital. There was a statistically significant relationship between the type of drug used and the frequency of adverse events observed ( $p = 0.0001$ ). The results showed that phenobarbital had more adverse effects, including renal and hepatic complications, whereas valproate had the highest adverse event with skin complications (41%). Valproate also had the least liver complication, which seems to be the best choice in patients susceptible to hepatic impairment. Phenobarbital also had a very mild skin reaction, making it a good choice in children prone to skin disorders. In a

2004 study by Loring et al., the cumulative effects of antiepileptic drugs in children were studied. In this study, as in our study, high skin complications were observed in patients taking valproate (12).

In our study antiepileptic drugs had no effect on platelet count but in all patients, leukocytosis was observed in all types of complications with the highest count of WBC in skin-related side effects. In a 2007 study by Banu et al., the side effects of antiepileptic drugs including phenytoin, carbamazepine, valproate, and phenobarbital were investigated in children. In this study, leukocytosis was observed in all patients who had a drug complication 2 days later. Also in this study, as in our study, the highest number of white blood cells was observed in the skin-related side effects (13).

## Conclusion

According to the findings of this study, it can be concluded that the renal side effects of antiepileptic drugs in males are higher than females; whereas the skin and liver complications are higher in females. The most common side effects are observed within the age range of 9 to 10 years. It has a direct relationship with the duration of drug side effects. Side effects with Phenobarbital are more common than with valproate.

## Conflict of interest:

The authors have no conflicts of interest in this work.

## Funding:

None.

## Acknowledgments:

We would like to appreciate all personnel involved in this study employed in Shahid Motahari Hospital of Urmia.

## References

1. Perucca E. The pharmacology of new antiepileptic drugs. Springer; 2011.

2. Gelisse P, Genton P, Kuate C, Pesenti A, Baldy - Moulinier M, Crespel A. Worsening of seizures by oxcarbazepine in juvenile idiopathic generalized epilepsies. *Epilepsy* 2004; 45 (10): 1282-6.
3. Zaccara G, Franciotta D, Perucca E. Idiosyncratic adverse reactions to antiepileptic drugs. *Epilepsy* 2007; 48 (7): 1223-44.
4. Yip V, Marson A, Jorgensen A, Pirmohamed M, Alfirevic A. HLA genotype and carbamazepine - induced cutaneous adverse drug reactions: a systematic review. *Clin Pharmacol Ther* 2012; 92 (6): 757-65.
5. Brodie MJ, Mintzer S, Pack AM, Gidal BE, Vecht CJ, Schmidt D. Enzyme induction with antiepileptic drugs: cause for concern? *Epilepsy* 2013; 54 (1): 11-27.
6. Perucca P, Gilliam FG. Adverse effects of antiepileptic drugs. *Lancet Neurol* 2012; 11 (9): 792-802.
7. Tomson T, Battino D. Teratogenic effects of antiepileptic drugs. *Lancet Neurol* 2012; 11 (9): 803-13.
8. Meador KJ, Loring DW. Risks of in utero exposure to valproate. *Jama* 2013; 309 (16): 1730-1.
9. Bosak M, Porębski G, Słowik A, Turaj W. Common allergies do not influence the prevalence of cutaneous hypersensitivity reactions to antiepileptic drugs. *Epilepsy research* 2017; 135: 9-13.
10. Senacom P, Jarernsiripornkul N, Uchaipichat V. Adverse Drug Reaction Monitoring to Antiepileptic Drugs by Patient Self-Reports. *Srinagarind Medical Journal* 2008; 23 (4): 373-82.
11. Herranz JL, Armijo JA, Arteaga R. Clinical side effects of phenobarbital, primidone, phenytoin, carbamazepine, and valproate during monotherapy in children. *Epilepsy* 1988; 29 (6): 794-804.
12. Loring DW, Meador KJ. Cognitive side effects of antiepileptic drugs in children. *Neurology* 2004; 62 (6): 872-7.
13. Banu SH, Jahan M, Koli UK, Ferdousi S, Khan NZ, Neville B. Side effects of phenobarbital and carbamazepine in childhood epilepsy: a randomized controlled trial. *Bmj* 2007; 334 (7605): 1207.