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RESEARCH ARTICLE

Adverse Drug Reactions of Anti-Epileptic Drugs in Children with Epilepsy: A Cross-Sectional Study

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Abstract: ***Background*:** Adverse drug reactions (ADRs) due to antiepileptic drugs (AEDs) in children contribute to poorer patient outcomes. However, reliable data ragarding such ADRs is not available.

***Objectives*:** Thus, the aim of the present study was to determine the incidence and patterns of ADRs of antiepileptic drugs in children aged 2-17 years presenting to a tertiary care teaching hospital.

***Methods*:** An observational study was conducted in the Department of Pediatrics, Kalawati Saran Children's Hospital for a period of one year. Two hundred consecutive eligible patients (aged 2-17 yrs with epilepsy on AED) with consenting parents were enrolled. ADRs were noted using Paediatric Epilepsy Side Effect Questionnaire (PESQ) at clinic visits and any other ADRs reported by parents were also recorded. Causality, severity and avoidability assessments were done.

***Results*:** The mean age was 10.5 ± 3.6 years. A total of 139 ADRs occurred in 97 patients. One hundred and nine ADRs were reported by use of PESQ, in addition, 30 ADRs were reported by parents. Poor school result (33.8%) was the commonest ADR. Valproate (61.9%) was the main drug causing ADRs. Valproate, when used in polytherapy, was associated with more number of children experiencing ADRs (72.2%). The most common add on drug was clobazam (42.3%). Children with poorly controlled epilepsy were associated with more ADRs. Causality assessment revealed that 91.3% of the ADRs were probable. Most (94.9%) ADRs were of 'mild' category and 95.7% were probably preventable. Treatment was discontinued only in 6 patients of phenytoin toxicity.

***Conclusion*:** Cognitive and neurological problems were the most common ADRs seen in children with epilepsy. Polytherapy significantly increases the likelihood of ADRs in children.

ARTICLE HISTORY

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1. INTRODUCTION

Pharmacotherapy constitutes the backbone of epilepsy treatment. The last two decades have observed a spectacular increase in the number of drugs available to treat epilepsy, with over seven newer Antiepileptic Drugs (AEDs) approved for use in children [1]. Treatment with antiepileptic drugs, however, is not without risks. Adverse effects can contribute to treatment failure in up to 40% of patients and can affect the ultimate quality of life independent of seizure control [2].

The adverse effects to AED may be dose-dependent and reversible, such as valproate induced thrombocytopenia or idiosyncratic reactions with life-threatening consequences such as Steven-Johnson syndrome and bone marrow suppression. Children on both old and new generation AEDs have cognitive and behavioural effects, which may sometimes be difficult to separate from the consequences of underlying epilepsy. Evidence from a study done in UK revealed that AEDs were the medication most likely to be associated with a fatal suspected Adverse Drug Reaction (ADR), [3] and data from a children's hospital over a 10-year period in the USA revealed that AEDs were associated with 23% of severe ADRs [4]. Therefore, ADRs are among the most important factors in choosing the appropriate AED for the patient. If two AEDs have similar efficacy, the frequency and type of expected drug toxicity are essential elements to decide which drug to use [5].

Most of the information about the ADRs associated with ADEs has been obtained from studies conducted in the adult population. Young children are often more susceptible to AED side effects and need special contemplation in relation

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to the prescribing of these drugs. The rapidly changing metabolism during early development can make AED use in children perilous [6]. Only a few epidemiological studies are available, which have explored the AED safety profile in pediatric patients. Thus, the present study was conducted to determine the nature and rate of adverse drug reactions of antiepileptic drugs in children with epilepsy aged 2-17 years presenting to a tertiary care teaching hospital.

2. MATERIALS AND METHODS

2.1. Study Design

This was a cross-sectional study conducted in the Department of Pediatrics at Kalawati Saran Children's Hospital, New Delhi from September 2015 to September 2016.

2.2. Methodology

Two hundred consecutive children of either sex, aged between 2 and 17 years diagnosed with epilepsy (idiopathic or symptomatic) on AED treatment for at least 3 months were screened from Epilepsy clinic. Children's with known Intellectual disability, global developmental delay, autism, attention deficit hyperactivity disorder, cerebral palsy and other pre-existing chronic systemic illness *e.g.* chronic renal or liver diseases were excluded from the study. Written informed consent was taken from the parents and assent was taken from children older than 7 years of age. The study was approved by the Institutional Ethics Committee, the Lady Hardinge Medical College Ethical Committee for Human Research (Approval no. LHMC/ECHR/2015/28).

Eligible participants underwent detailed clinical assessment as per clinical performa and details of epilepsy, such as age of onset of epilepsy, duration of epilepsy, type of epilepsy, etiology, AED treatment regimen, were recorded. Adverse drug reactions were noted using Pediatric Epilepsy Side Effect Questionnaire (PESQ) at clinic visits and any other adverse drug reaction reported by parents were noted. Each patient was evaluated only once unless there were patient/parent reported ADR during subsequent visits. The current adverse effects at the time of the visit were also noted.

The PESQ is a 19-item validated measure which assesses the side-effects of AEDs, it consists of 5 subscales: cognitive (6 items), motor (4 items), behavioral (3 items), general neurological (4 items), and weight (2 items) related side-effects [7]. The cognitive scale assessed slow thinking, memory problems, confusion, poor school results, decreased concentration, and attention difficulties. The motor scale assessed unstable walking, poor coordination or clumsiness, falling (not related to seizures), and speech difficulties. The behavioral scale assessed aggression, hyperactivity, and personality change.

The general neurological scale assessed drowsiness or sleepiness, fatigue or tiredness, dizziness or lightheadedness, and headache. The weight scale assessed increase in appetite and weight gain. Items (adverse effect) were rated on a 6-point Likert scale ranging from 1 (not present) to 6 (high severity). Scaled scores were calculated for the five subscales and finally, summary score or total side effects score was a compilation of the 5 core subscales. Scores ranged from 0 (no side effects) to 100 (highest level of side effects).

The causality relationship between the suspected ADRs and the medications was assessed using Naranjo probability scale [8]. Hartwig's severity scale [9] was used to assess the severity of ADRs and modified Schumock and Thornton criterion [10] was used to assess the preventability of the ADRs.

2.3. Outcomes

The primary objective of the study was to assess the incidence and pattern of adverse drug reactions. The secondary objective was to assess the correlation of ADRs with age, sex and epilepsy type, frequency of ADRs in monotherapy v/s polytherapy, and proportion of preventable ADRs.

2.4. Statistical Analysis

The data was entered in an excel sheet and statistical analysis was done using SPSS software version 20 (SPSS Software Inc., Chicago, IL, USA). Descriptive statistics (mean/standard deviation (S.D)/percentages) were used to describe the characteristics. Baseline parameters were compared by student unpaired t-test, chi-square test or Fisher exact test. $P<0.05$ was taken as significant.

3. RESULTS

3.1. Demographic Profile of Patients Enrolled

A total of 200 children's were enrolled, the mean age being 10.5 (SD 3.6) years. 117 (58.5%) patients were male whereas 83 (41.5%) patients were female. The mean age at seizure onset was 7.5 (SD 3.7) years. Distribution of epilepsy patients according to age group and sex is presented in Table **1**. The mean duration of epilepsy was 3.0 (SD 2.8 years). The distribution of epilepsy patients according to etiology as per International League Against Epilepsy (ILAE) 2010 is depicted in Table **2**. Generalized seizures were found in 134 (67%) patients followed by focal seizures in 58 (29%). Focal seizures evolving to bilateral convulsive were found in 7 (3.5%) patients. Absence seizures were found in 4 (2%) patients. Mixed types of seizures were found in 8 (4%) patients.

3.2. Prescribing Pattern of Drugs

Majority of patients 174 (87%) were on monotherapy whereas 26 (13%) were on polytherapy. Valproate was the commonest drug prescribed as monotherapy in 84 (48.3%) followed by phenytoin in 62 (35.6%) (Fig. **1**). Combination of valproate and levetiracetam, valproate and clobazam and phenytoin & clobazam was used in five (19.2%) patients each (Fig. **2**). The most common add on drug used in polytherapy was clobazam in 11 (42.3%) patients followed by levetiracetam in 6 (22.0%), valproate in 4 (15.4%), carbamazepine in 3 (11.5%), phenytoin in 1 (3.8%), and topiramate in 1 (3.8%) patients.

3.3. Characteristics of Patients with Adverse Drug Reactions

A total of 139 suspected ADRs occurred in 97 patients. The majority (98%) of the suspected ADRs were type A (drug dose-related) whereas only 4 (2%) were type B (idio syncratic).

Table 1. Distribution of epilepsy patients according to age group and sex.

Characteristics (N=200)		N (%)
Age groups	Less than 5 years	23 (11.5%)
	6 to 10 years	75 (37.5%)
	More than 10 years	102 (51.0%)
Sex	Males	117 (58.5%)
	Females	83 (41.5%)

Table 2. Distribution of epilepsy patients according to etiology as per ILAE 2010.

Etiology	Diagnosis	N (%)
Infections	Neurocysticercosis	99 (49.5%)
	Tuberculoma	3 (1.5%)
	Post meningitic sequalae	2 (1.0%)
Epilepsy syndromes with presumed genetic basis	Generalized epilepsy	57 (28.5%)
	Rolandic	19 (9.5%)
	Childhood absence epilepsy	5 (2.5%)
	Juvenile myoclonic epilepsy	4 (2.0%)
	Juvenile absence epilepsy	4 (2.0%)
	Genetic epilepsy with febrile seizures	2 (1.0%)
Structural	Structural	5 (2.5%)
-	Total	200 (100.0%)

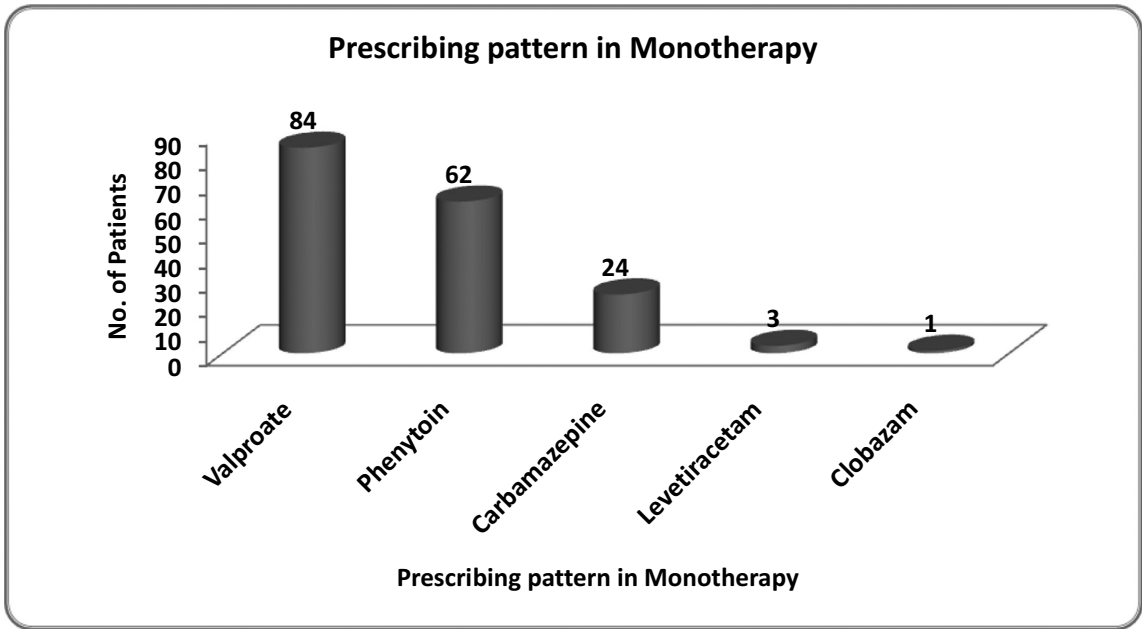

Fig. (1). Prescribing pattern of antiepileptic drugs in monotherapy.

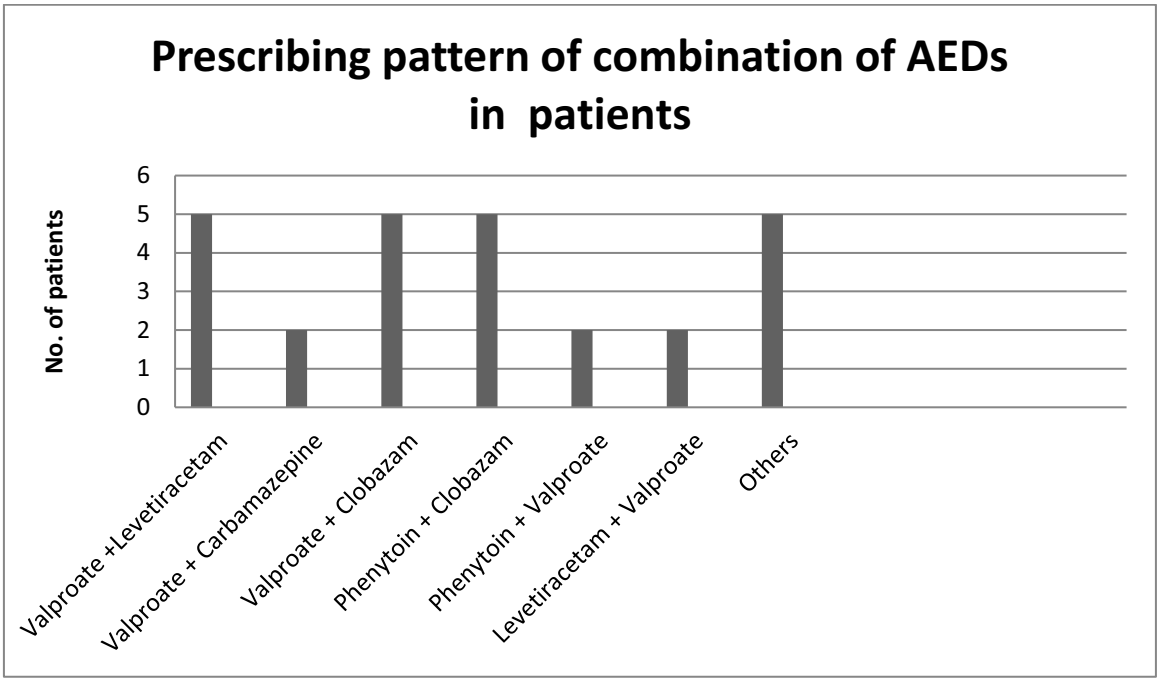

Fig. (2). Prescribing pattern of combination of antiepileptic drugs in patients**.**

*The graph shows the first drug on which the patient was started followed by the add on drug.
**Other combinations like: valproate & phenytoin, phenytoin & carbamazepine, carbamazepine & clobazam, valproate & topiramate and phenytoin & levetiracetam were used in one patient each.

Among the patients who developed the suspected ADRs, 55.4% were female and 43.6% were male. This distribution of proportions was found statistically nonsignificant (p=0.09).

Majority of the childrens (58) with ADRs were in the age group more than 10 years followed by 35 children in age group 6 to 10 years & 4 children in the age group less than 5 years. This distribution of proportions was found statistically significant (p<0.05). Polytherapy was associated with more ADRs than monotherapy. 73.1% patients on polytherapy developed ADRs while 44.8% patients who were on monotherapy developed ADRs (p<0.05).

More than half 73(59.3%) of the children with ADRs were having poorly controlled epilepsy (multiple seizures), while well-controlled epilepsy was present in 24 (31.2%) children with ADRs. This distribution of proportion was found statistically significant (p<0.05). Among children with ADRs, in majority *i.e.* 69 (71.1%) patients, duration of epilepsy was more than a year whereas in 28(28.9%) patients, duration of epilepsy was less than a year (p<0.05).

3.4. ADRs as per Pediatric Epilepsy Side Effect Questionnaire (PESQ)

ADRs noted using PESQ were 109 (78.5%) (Fig. **3**). While studying ADRs as per PESQ, among cognitive functions, a total of 55 ADRs occurred out of which 34 were caused by valproate. Poor school results were the commonest cognitive ADRs found in 47 patients out of 55 patients. Among motor functions, 2 ADRs occurred one each caused by valproate and phenytoin. Among behavioral functions, 5 ADRs occurred, all were caused by valproate. Among general neurological functions, 41 ADRs occurred, amongst which 24 were caused by valproate followed by phenytoin (10). All 6 cases of weight gain were caused by valproate (Tables **3**-**5**).

3.5. Other Adverse Drug Reactions Reported by the Patients/Parents

Among total 30 (21.5%) ADRs reported other than PESQ, the majority (11) were nocturnal enuresis followed by 7 cases of alopecia, (Table **6**). Sixteen ADRs were caused by valproate out of which nocturnal enuresis (8) was the most common.

Overall (ADRs as per PESQ and others reported) **t**he Cognitive ADRs (39.5%) were commonly followed by general neurological ADRs (29.5%).

3.6. Antiepileptic Drugs Causing ADRs (as per PESQ and others)

In the present study, overall valproate (86/139=61.9%) was the main drug causing ADRs. Much lesser ADRs were seen with carbamazepine (9.4%) (Table **7**).

Valproate, when used in polytherapy, was associated with more number of children with ADRs (72.2%) than in monotherapy (56.0%). Phenytoin was also associated with more number of children with ADRs in polytherapy (70.0%) than monotherapy (33.9%).

3.7. Causality Assessment

In the present study according to Naranjo probability scale, the relationship between the ADRs and the respective drugs was under “probable” category in 91.3% followed by possible in 8.7%.

Table 3. Cognitive ADRs with anti epileptic drugs (PESQ).

ADR Related ONLY to Seizure Medicine	Valproate N =86	Phenytoin N=36	Carbamazepine N=13	Levetiracetam N=4
A Cognitive				
1. Slow thinking	2 (2.3%)	0	1 (7.7%)	0
2. Memory problems	3 (3.5%)	1 (2.77%)	0	0
3. Confusion	0	0	0	0
4. Poor school results	28 (32.5%)	11 (30.5%)	5 (38.5%)	3 (75%)
5. Decreased concentration	1 (1.16%)	0	0	0
6. Attention difficulties	0	0	0	0
Total	34 (39.5%)	12 (33.3%)	6 (46.2%)	3 (75%)

Table 4. Motor and behavioural ADRs with anti epileptic drugs (PESQ).

ADR Related ONLY to Seizure Medicine	Valproate N=86	Phenytoin N=36	Carbamazepine N=13	Levetiracetam N=4
B. Motor				
7. Unstable walking	0	1 (2.77%)	0	0
8. Poor coordination, clumsiness	0	0	0	0
9. Falling (not seizure)	0	0	0	0
10. Speech difficulties	1 (1.16%)	0	0	0
Total	1 (1.16%)	1 (2.77%)	0	0
C. Behavioral				
11. Aggression	4 (4.65%)	0	0	0
12. Hyperactivity	1 (1.16%)	0	0	0
13. Personality change	0	0	0	0
Total	5 (5.8%)	0	0	0

Table 5. General neurological and weight related ADRs with AEDs (PESQ).

ADR Related ONLY to Seizure Medicine	Valproate N=86	Phenytoin N=36	Carbamazepine N=13	Levetiracetam N=4
D. General neurological				
14. Drowsiness, sleepiness	22 (25.6%)	7 (19.4%)	6 (46.2%)	1 (25%)
15. Fatigue, tiredness	1 (1.16%)	0	0	0
16. Dizziness, lightheadedness	0	1 (2.77%)	0	0
17. Headaches	1 (1.16%)	2 (5.55%)	0	0
Total	24 (27.9%)	10 (27.7%)	6 (46.2%)	1 (25%)
E. Weight				
18. Increase in appetite	0	0	0	0
19. Weight gain	6 (6.97%)	0	0	0
Total	6 (6.97%)	0	0	0

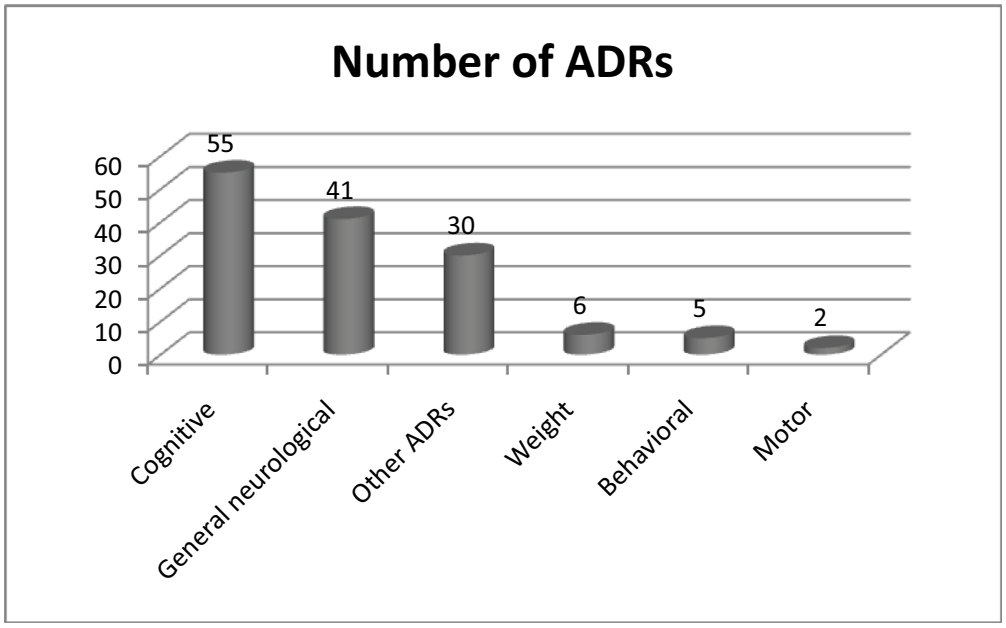

Fig. (3). ADRs as per PESQ and others reported by patient.
* ADRs noted using PESQ were 109 distributed under different categories.
**Other ADRs are the ADRs reported by the parents.

Table 6. Other ADRs with anti epileptic drugs.

ADR Related ONLY to Seizure Medicine	Valproate N=86	Phenytoin N=36	Carbamazepine N=13	Levetiracetam N=4
1. Nocturnal Enuresis	8 (9.3%)	2 (5.55%)	1 (7.7%)	0
2. Alopecia	6 (6.97%)	1 (2.77%)	0	0
3. Hirsutism	1 (1.16%)	0	0	0
4. Tremor	1 (1.16%)	0	0	0
5. Gum Hypertrophy	0	3 (8.33%)	0	0
6. Loss of Appetite	0	1 (2.77%)	0	0
7. Toxicity (ataxia, nystagmus etc.)	0	6 (16.6%)	0	0
Total	16 (18.6%)	13(36.11%)	1 (7.7%)	0

Table 7. ADRs (total) by antiepileptic drugs.

ADR Related ONLY to Seizure Medicine	Valproate N=86	Phenytoin N=36	Carbamazepine N=13	Levetiracetam N=4
A. Cognitive	34 (39.5%)	12 (33.3%)	6 (46.2%)	3 (75%)
B. Motor	1 (1.16%)	1 (2.77%)	0	0
C. Behavioral	5 (5.8%)	0	0	0
D. General neurological	24 (27.9%)	10 (27.7%)	6 (46.2%)	1 (25%)
E. Weight	6 (6.97%)	0	0	0
F. Other ADRs	16 (18.6%)	13 (36.1%)	1 (7.7%)	0
Total	86 (100.0%)	36 (100.0%)	13 (100.0%)	4 (100.0%)
Percentage of total (139)	61.9%	25.9%	9.3%	2.9%

3.8. Severity

As per Hartwig & Siegel severity assessment scale, the relationship between the ADRs and the respective drugs was under "mild" category in 94.9% followed by moderate in 5.1%. Except 7, the treatment with AED was continued in all the patients who reported adverse effects. In 6 cases, treatment with phenytoin was stopped as it caused toxicity and in one treatment was stopped as a result of valproate-induced alopecia.

3.9. Preventability

As per Schumock and Thornton preventability assessment scale, 95.7% of ADRs were "probably preventable" followed by definitely preventable in 4.3%.

4. DISCUSSION

A large number of drugs are currently available for the treatment of epilepsy. Older/conventional drugs like phenytoin, carbamazepine, valproate and ethosuximide are commonly used as first-line drugs. They are relatively less expensive than the newer antiepileptics and easily available in hospital pharmacy free of cost. Drugs like gabapentin, lamotrigine, vigabatrin, topiramate, tiagabine and zonisamide are the newer ones and currently used as add-on or alternative therapy. They have lesser adverse effects and have few, if any, drug interactions [11, 12].

Monotherapy is the usual aphorism, but polytherapy is needed for patients with multiple seizure types or refractory disease [13, 14] In the present study, monotherapy (87%) was the commonly used therapeutic approach followed by polytherapy (13%) which is similar to other studies in which monotherapy was used predominantly [15-17].

In the present study, the most commonly used AED was sodium valporate (49%) followed by phenytoin (35.5%). The findings of the present study were in conformity with the findings of Kousalya *et al*. [17], who found the most common drug to be sodium valporate (37.02%) followed by phenytoin (23.83%) and Anderson *et al*. [16] found valproate (33%) followed by carbamazepine (25%) as the most common AED causing ADRs. In contrast to the present study, Bansal *et al*. [6] and Mathur *et al*. [18] found phenytoin as the most common drug used. Clobazam (37%) followed by phenytoin (25.5%) was found as the commonest drug used in a study by George *et al*. [19].

In the present study, ADRs were found in 48.5% of children's. Anderson *et al*. [16] and Mistry *et al*. [20] observed ADRs in 31% & 26% of children, respectively. In contrast to the present study the incidence of ADRs was much higher (63.2%) in a study by Bansal *et al* [6]. In another study by Kousalya *et al*. [17] the overall incidence of ADRs was found to be very low (5.3%). This may be due to different study population and/or adoption of different study methodology.

Majority of children with ADRs were in the age group of more than 10 years, similarly to this Bansal and coworkers also found that children developing ADRs with AED therapy were significantly older [6].

In the present study, 43.6% males developed ADRs while 55.4% females developed ADRs. Bansal *et al.* [6] also found a higher frequency of ADRs in girls (71.3%) than boys (57.4%). But other studies found boys developing more ADRs than girls [17-21].

Poor school results (33.8%) was the commonest adverse drug reaction followed by drowsiness (25.9%) as the second common ADR. This finding is comparable with findings of Bansal *et al*. [6] who found poor school results (19%) as the most prevalent ADR followed by gum swelling (13%) and drowsiness (5.7%). Anderson *et al*. [16] showed behavioral problems (19.3%) as the most common ADR of AEDs followed by somnolence (15.8%). In contrast to the present study, in a study by Mistry *et al*. [20] irritability was the most prevalent ADR (32.2%) followed by drowsiness (18.6%).

Valproate-induced nocturnal enuresis was found in 11 patients. Some studies evaluating the adverse events associated with valproate mentioned enuresis as a side effect of this drug with a frequency, when reported, ranging between 2% and 7% [22, 23]. The mechanism of enuresis is believed to be multifactorial and includes sleep disorders, genetic factors, decreased functional bladder capacity, and the absence of circadian nocturnal rise in the secretion of the antidiuretic hormone.

Gum hypertrophy was less in the present study, this can be attributed to the fact that, that all patients received folic acid supplementation along with phenytoin which is supposed to lower the risk of gum hypertrophy. In a study done by Bansal *et al.* [6] and Mathur *et al*. [18], gum hypertrophy was more because phenytoin was commonly used AED in their studies.

In the present study as per the PESQ majority of the patients had cognitive side effects, followed by general neurological side effects, weight changes, behavioral and motor side effects. In concordance to this, a study by Junger *et al.* [24] using the same questionnaire also revealed that majority of patients suffered behavioral (mean=14.1) followed by general neurological side effects (mean=13.9), cognitive (mean=13.3).

Valproate was the main drug leading to poor school results followed by phenytoin and carbamazepine. This finding is in accordance with the findings of Bansal *et al.* [6]. Polytherapy was associated with more ADRs than monotherapy 73.1% patients on polytherapy developed ADRs while 44.8% patients who were on monotherapy developed ADRs. Similar, to the present study Anderson *et al*. [16] showed that 60% on polytherapy and 21% on monotherapy experienced ADRs. Whereas Bansal *et al.* [6] found no significant difference in ADRs between monotherapy and polytherapy.

According to Naranjo algorithm, the relationship between the ADRs and the respective drugs was found to be "probable" in 91.3% followed by possible in 8.7% which is analogous to the findings of a study done by Bansal and coworkers. On the contrary, in a study by Mistry *et al.* [20], the relationship between the ADRs and the respective drugs was "possible" in 103 (87.3%). This can be attributed to the use of different scale (WHO causality assessment scale) for assessing the causality in the study.

On severity assessment according to Hartwig severity scale 132 ADRs (94.9%) were categorized as mild, and 7 (5.1%) were found to be of moderate severity. The finding is similar to Mistry *et al*. [20] Whereas in a study by Anderson *et al*. [16] 61% were categorized as moderate. This can be attributed to different scales used to categorize.

Majority of ADRs (95.7%) were "probably preventable". Similarly, Mistry *et al*. [20] reported that the majority of ADRs were preventable (98.3%) as per Schumock and Thornton preventability assessment scale.

5. LIMITATIONS OF THE STUDY

The limitations of the study include small sample size and use of self/parental reporting of the ADRs. No formal tests of psychometric and intelligence quotient assessment were used. Also, in the context of cognitive and behavioral side effects, the causation may also include underlying epilepsy in addition to the AED. Past school records were not checked to see school performance.

CONCLUSION

The present study demonstrates that ADRs are relatively common in the pediatric population with epilepsy. Behavioral problems and somnolence were the most common ADRs. Polytherapy significantly increases the likelihood of ADRs in children.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

This study was approved by the Institutional Ethics Committee, the Lady Hardinge Medical College Ethical Committee for Human Research (Approval no. LHMC/ECHR/2015/28), India.

HUMAN AND ANIMAL RIGHTS

No animals were used in the study. All reported experiments on humans were in accordance with the ethical standards of the committee responsible for human experimentation (institutional and national), and with the *Helsniki Declaration* of 1975, as revised in 2008 (http://www.wma.net/en/20activities/10ethics/10helsinki/).

CONSENT FOR PUBLICATION

Written informed consent was taken from the parents and assent was taken from children older than 7 years of age.

FUNDING

None.

CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

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Declared none.

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