ORIGINAL RESEARCH

A study on detrimental effect of antiepileptic drugs dose in pediatric children

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ABSTRACT
Introduction: Adversity of epileptic drugs is still unwanted and inseparable along with advantages of epileptic medication, despite much progress has been made in the area of anti-epileptic drugs (AEDs) development. Therefore, the aim of this study was to compare the effectiveness of AED under BNF guidelines and regular practice for different oral antiepileptic medications in enhancing and controlling the patient's disease state and tolerability.
Material and Methods: All the patients (70) were randomly divided into two groups; group I patients were on regular practice medication While, group II patients followed British National Formulary (BNF) guideline. The Pediatric Quality of Life Inventory (PedsQL) was used to assess the adverse effects in epileptic patients.
Results: Results revealed that 23.5% patients of Group II patients followed BNF had seizures whereas, 53.1 % patients of group I who followed regular practice had convulsion after 6 months follow up. Patients on levetiracetammonotherapy were experiencing poor seizure control with a number of seizure incidence in group I patients (n=10) compared to patients (n=4) who followed the BNF guidelines. Adverse effects were more in 65.6% patients of group I following regular practice medicines (n=21) compare to 23.5% patients (n=8) of group II followed BNF guidelines.
Conclusion: The present study concluded that unbiased individualization of patients for the selection AEDs and its doses according to BNF guidelines has been found significantly effective in reducing the adverse effects as well as improved seizure control in pediatric population.
Key Words: Epilepsy, AEDs, Titration, Pediatrics.

INTRODUCTION
Worldwide, epilepsy is considered as the most common neurological disorder with the prevalence of 144 out of 100000 in infants (1 to 12 months age); whereas, it is lower up to 58 per 100000 for children (1 to 12 yrs age). [1] In India incidence of epilepsy in children (6.5 per 1000 children/yr) was very similar to the western countries; Prevalence of epilepsy was twice in children compare to middle age people. [2] Epilepsy is repetition of at least two reflex seizures that necessitate an alteration in patient's level of consciousness (both motor and sensory) without any provoking cause. [3]

In spite of various side effects Phenobarbital (PB) was established as gem of medicine for the treatment of epilepsy in the early 20th century till date; Adversity of epileptic drugs is still unwanted and inseparable along with advantages of epileptic medication, despite much progress has been made in the area of anti-epileptic drugs (AEDs) development. [4]

Presently, two generations of AEDs are in use. The old generation is represented by drugs like; Valproate (VPA), Carbamazepine (CBZ), Phenytoin (PHT), Primidone (PRM), and Phenobarbital (PHB). While the new generation includes: Lamotrigine (LMT), Levetiracetam (LVT), Oxcarbazepine (OXC), Topiramate (TPM), Clonazepam (CLNZ), Vigabatrin (VGB), Pregabalin (PGB), Rufinamide (RFM), and Lacosamide(LAC). [5]

Various concentration related adverse effects of epileptic drugs like blurred vision, dullness, dizziness, drowsiness, ataxia etc have been found especially in children; however, these ill effects are mostly brief and mild which can be resolve by altering the quantity or direction of drugs used. [6] There are studies suggesting that various social, psychological, learning and behavioural ailments have been found associated as co-morbidity to AEDs. [7, 8] AEDs have shown negative effects on routine functioning as well as well being of patients; moreover, severity of adverse effects are directly related to the time duration of epileptic drugs uses. [8, 9]

Delayed drug absorption, increase central nervous system permeability to certain drugs (e.g. PHT) lead to increase in effect or toxicity, increase in total body water and decrease in binding capacity of drugs towards plasma proteins (e.g. PHB, PHT, VPA), augment the risk of adverse effects due to the build-up of the drug in the system can be the result of prolonged gastric emptying. Similar effects can be induced by decrease rates of hepatic metabolism in neonates and increased activity of hepatic microsomal enzymes in children especially between 2-4 years of age due to relatively larger liver size in comparison to total body weight which require a higher maintenance doses compared to adult. These side effects were found to be more marked among patients on older AEDs in comparison to them on new AEDs. [5, 6]

British National Formula (BNF) guidelines emphasis on the individualization of patients for the unbiased and exact drug prescription to decrease the incidence of seizures along with minimum adverse effects compare to traditional way of prescription of drugs randomly without individualization. [10]

A lack of guidance regarding initiation and dose titration of AED mono therapies or novel adjunctive AEDs into poly therapy regimen is still a major concern in pediatric population. [11]

Therefore, the aim of this study was to compare the effectiveness of AED under BNF guidelines and regular practice for different oral antiepileptic medications in the PSMMC formulary (Older generation -VPA, CBZ, PHT, PRM, OXC, PHB and New generation - LMT, LVT, OXC, TPM, CLNZ, VGB, PGB, RFM, LAC) in enhancing and controlling the patient's disease state and tolerability. The subsidiary targeted outcome was to improve the safety of antiepileptic drugs by lessening the side effect with a gradual dose titration.

MATERIAL AND METHODS

The type of antiepileptic drugs was classified into conventional AEDs (1st generation) and newer AEDs (2nd generation). The conventional AEDs which were prescribed in the PSMMC include: VPA, CBZ, PHT, PRM and PHB. While the newer AEDs prescribed were: LMT, LVT OXC, TPM, CLNZ, VGB, PGB, RFM, and LAC. Types of seizures were classified based on the International League against Epilepsy classification into three main types: focal (partial) seizures, generalized seizures and undetermined whether focal or generalized seizures.

STUDY POPULATION

All the patients were randomly divided into two groups; group I had thirty five patients (35) followed regular practice medication; while group II consisted thirty five patients (35) which

were on British National Formulary (BNF) guideline. [10] All the patients were monitored for the safety and efficacy of their antiepileptic drugs each visit.

INCLUSION AND EXCLUSION CRITERIA
A medical record of pediatric patients below 14 years old who have been newly diagnosed with epilepsy or on a new epileptic treatment plan (such as: increasing the dose of current antiepileptic drug or adding a novel antiepileptic drug to the treatment regimen) were enrolled in the study regardless of the type, gender, and ethnicity. Whereas, patients of more than fourteen years age and those on antiepileptic drugs for other reasons than to control seizure were excluded from the study. The epileptic cases were diagnosed in the hospital by medical specialist and then referred to pediatric neurology department. The parents were subsequently requested to indicate their approval for their children to enter this study by signing a dated consent form.
Subsequent follow-up such as current anticonvulsant(s) with the doses and formulation, any changes to the treatment plan (either increasing the dose of current antiepileptic drug or adding a new antiepileptic drug to the treatment regimen) were filed.
The Paediatric Quality of Life Inventory (PedsQL) [12] marker of health related quality of life (HQRL) was used to assess the adverse effects in epileptic patients. Arabic version of PedsQL was used to assess the quality of life in epilepsy children. [13] All the patients and their parents were explained in detail about this questionnaire before the study.

STATISTICAL ANALYSIS
All the results were expressed in numbers and percentage. The data was analyzed by using Microsoft Excel database. The data analyses focused on the presentation of descriptive statistics. SPSS 2.1 v manufactured by USA was used for data computation of PedsQL and the p value <0.05 was considered as statistically significant.

RESULTS
Present study included total seventy (70) children suffering with epilepsy for different duration. Group I patients (35) pursued the regular practice in the titration process which did not follow any specific guideline; while, group II patients (35) followed the BNF guideline. However, three (3) patients of group I while one (1) patient of group II left the study due to different reasons.
Fig1 shows that total ten (10), twelve (12) and ten (10) children of age groups up to 5 years, 6 to 10 years and 11 to 14 years respectively on regular practice. Further, twelve (12), fourteen (14) and eight (8) children belonging to age groups up to 5 years, 6 to 10 years and 11 to 14 years correspondingly followed BNF guidelines.
Fig 1: Age, gender details of patients following regular antiepileptic drug therapy and BNF guidelines
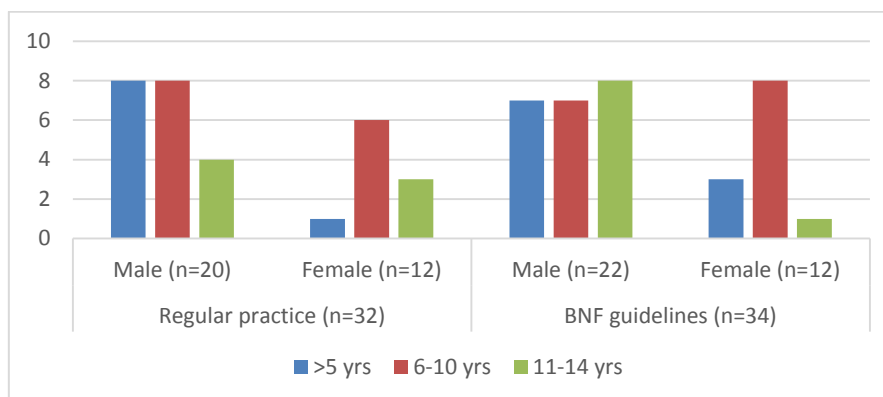
The distribution of drugs used for total sixty six (66) children on AEDs prescription was as following levetiracetam (n=22), lamotrigine (n=2), valproate (n=8), topiramate (n=12), carbamazepine (n=7), oxcarbazepine (n=4), phenytoin (n=2), phenobarbital (n=5) and rufinamide (n=2). Patient characteristics were generally consistent across index AEDs groups, exceptions with a lower number of included patients that were younger than 12 months; the proportion of males was slightly higher than the female by 1.66:1. The number of patients who followed the BNF was thirty four (34) on individualized AEDs compared to thirty two (32) patients who followed the regular practice. Fourteen (14) out of thirty one (31) of group I were on levetiracetam; whereas, eight (8) patients were on levetiracetam of individual AED prescription of group II. Topiramate was the most prescribed drug in group II patients on BNF guidelines. (Table 2)

Table 2: Baseline characteristics of patients with incidence of seizure and adverse effects.

Baseline Characteristics		Total Patients n=66	LVT (n=22)	LMT (n=2)	VPA (n=8)	TPM (n=12)	CBZ (n=7)	OXC (n=4)	PHT (n=2)	PHB (n=5)	RFM (n=2)
Age	1-12 months	4	2	0	0	1	0	0	0	1	0
	1-7 years	31	12	1	4	5	2	3	2	2	0
	8-14 years	29	8	1	4	6	5	1	0	2	2
Gender	Female	24	6	1	3	5	3	1	1	3	1
	Male	40	16	1	5	7	4	3	1	2	1
Epilepsy diagnosis	Partial seizure	18	7	0	2	4	2	1	0	1	1
	Generalized Seizure	20	8	2	1	1	3	1	1	3	0
	Other seizure Type	7	2	0	1	2	1	0	1	0	0
	Unclassified	19	5	0	4	5	1	2	0	1	1
Treatment guidelines	Followed the BNF	34	8	1	5	9	5	2	0	3	1
	Followed the practice	32	14	1	3	3	3	2	2	3	1

LVT – Levetiracetam, LMT – Lamotrigine, VPA – Valproate, TPM – Topiramate, CBZ – Carbamazepine, OXC – Oxcarbazepine, PHT – Phenytoin, PHB – Phenobarbital, RFM – Rufinamide.

The most prescribed medication in group II (BNF) were topiramate (n=12), levetiracetam (n=7), carbamazepine (n=5), and valproic acid (n=5). The physician was prescribing topiramate 0.5 – 1 mg/kg once in a day (max. per dose 25 mg), carbamazepine for 1-17 years of age a 100-200mg BID, valproic acid 10 – 15 mg per kg daily in divided dose and levetiracetam as adjunctive therapy of 10 mg/kg once daily then increased in steps up to 10

mg per kg twice daily (max. per dose 30 mg/kg) according to BNF guideline recommendation. (Table 3)

Table 3: Dose information and its side effects of antiepileptic drugs in children according to BNF guidelines.

Drugs	Initial dose (mg/kg/day)	Maintenance (mg/kg/day)	Daily doses (no.)	Side effects
Levetiracetam	10	20-60	2	Headache, anorexia, somnolence, behavioural Problems
Lamotrigine	0.5	2.0-10.0	2	skin rash, somnolence, dizziness, nausea
Valproate	0.2	1.0-5.0	2	Diarrohoea, Wt. gain, headache
Topiramate	1	6.0-9.0	2	Wt. loss, lethargy, anorexia
Carbamazepine	1	5.0-10.0	2	Dizziness, loss of appetite, ataxia, somnolence
Oxcarbazepine	5.0-8.0	10.0-30.0	2	Dizziness, ataxia, somnolence
Phenytoin	1.5	5.0-10.0	2	Cardiovascular risk, dermatoxic reaction, hepatic injury
Phenobarbital	15	5.0-10.0	2	Dizziness, ataxia, somnolence, headache, aggression
Rufinamide	10	1.0-5.0	1	CNS reaction, hypertension, multiorgan sensitivity, Leucopenia

It is evident from fig 1 that 23.5% patients followed BNF had seizures whereas, out of 32 patients followed regular practice 53.1% patients had convulsion after 6 months follow up. Further, results revealed that after 6 months of follow up patients on levetiracetam had fseizures in 4 patients (50%) out of 8 patients of group II on BNF guidelines compare to incidence of seizures in 10 patients (71.4%) out of 14 patients on levetiracetam of group I with the regular practice. Patients on levetiracetammonotherapy were experiencing poor seizure control with a number of seizure incidence in group I patients (n=10) compared to patients (n=4) who followed the BNF guidelines.
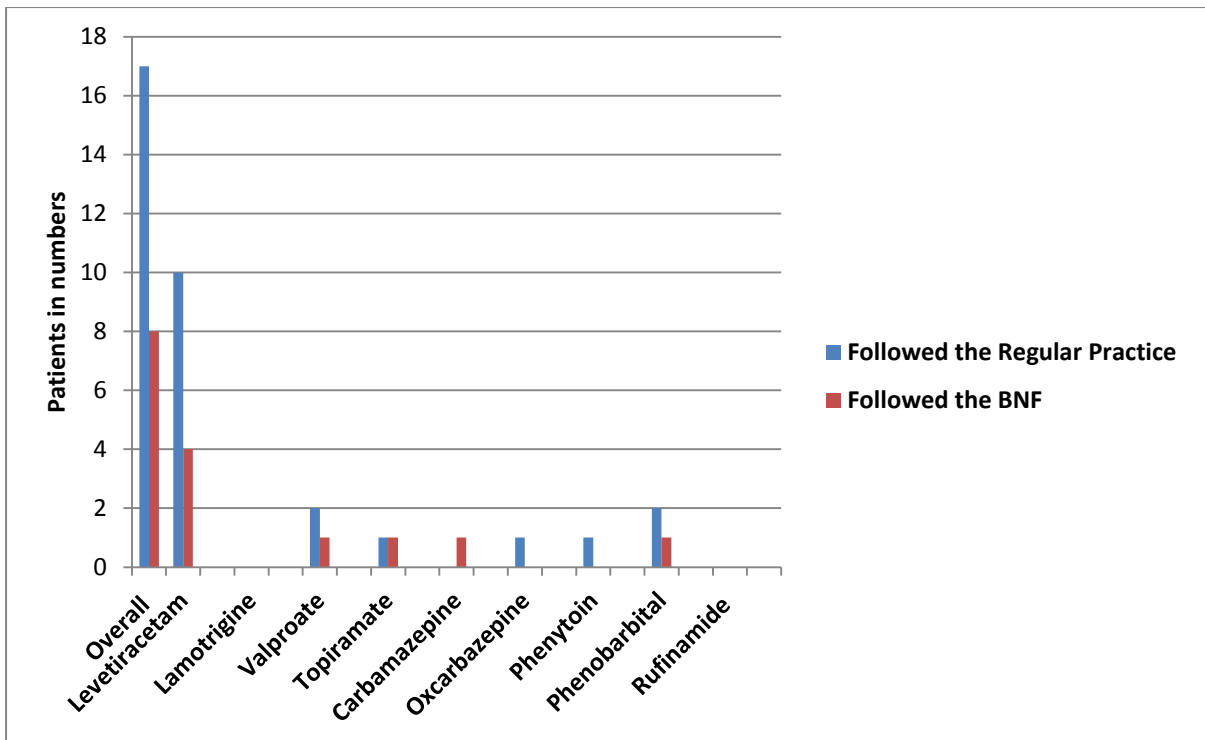
Fig 1: Patients treatment with incidences of seizures during treatment.

Fig 2 shows that adverse effects were more in 65.6% patients of group I following regular practice medicines (n=21) compare to 23.5% patients (n=8) of group II followed BNF guidelines. Patients that were on topiramate had minor headache, little psychomotor slowing and no speech problems. Comparing to the physician used a random guideline based on his/her preference; patients were experiencing fewer side effects while maintaining seizure control. The patient using a combination therapy of phenytoin and levetiracetam were experiencing some behavioral disturbance and sedation effect due to the synergistic side effect of this combination. (Fig. 2)
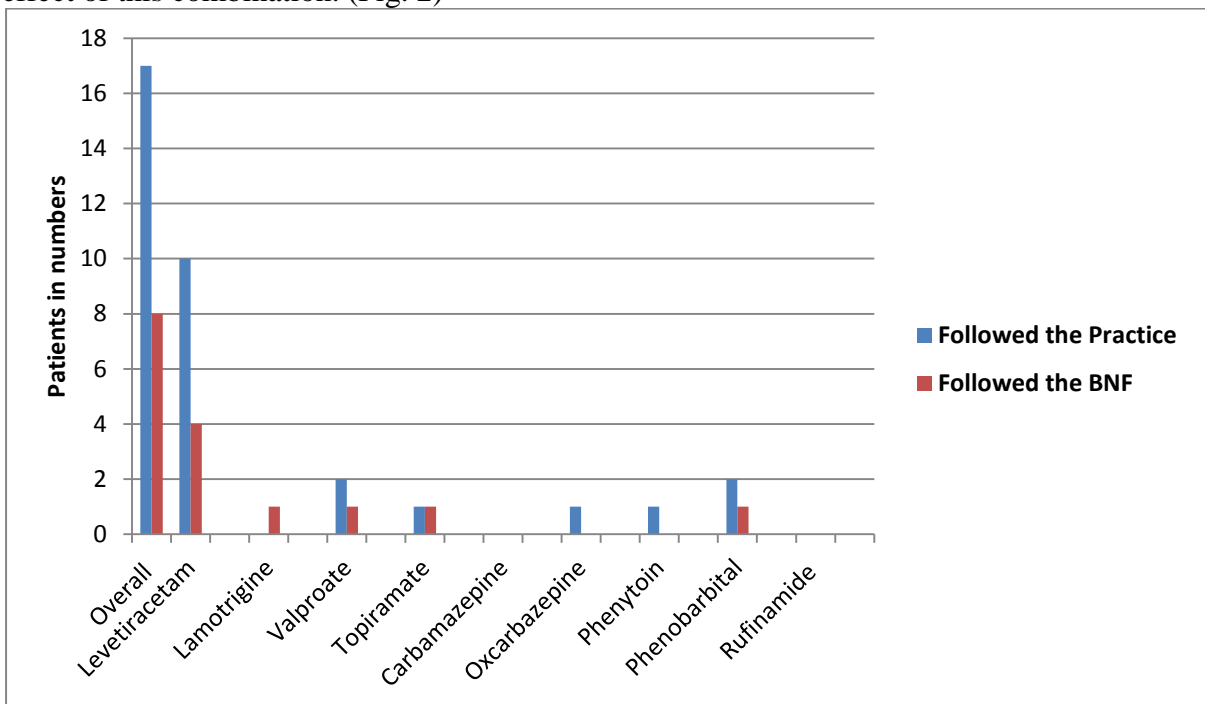

Fig 2: Number of patients with incidence of side effects.

Table 4 shows that there was decrease of in score of PedsQL score of group I patients on routine practice for physical, psychological and overall functioning; whereas, there was an insignificant difference in PedsQLscore of group II patients in BNF guidelines physical, psychological and overall functioning.

Table 4: Pediatric Quality of Life Inventory (PedsQL) scores in both groups before and after six months.

Parameters	Group I (Routine practice)			Group II (BNF)		
	Before	After	P value	Before	After	P value
Physical Functioning	80.3±16.4	74.9±18.6	<0.05*	79.8±19.7	80.5±20.6	>0.05NS
Psychological Functioning	76.6±20.7	71.7±17.2	<0.05*	76.2±18.3	77.9±16.6	>0.05NS
Overall functioning	77.8±13.8	72.5±14.4	<0.05*	78.1±14.6	79.2±15.7	>0.05NS

Values expressed as Mean+/-SD. *= Significant, NS= Non-significant.

Discussion

Various AEDs with different mechanism of action are successfully in use for the treatment of epilepsy in children irrespective to their side effects. [11] Diverse studies showed that AEDs have mild to severe side effects in children regardless to time duration of their anti-convulsion medicines consumptions. [14, 15]

Present study was an effort to assess the to and fro of different perspective on managing an effective therapeutic control of the disease along with safety and tolerability in the light of diverse antiepileptic studies that specifically examined the relationship between pediatric population and AEDs. [15, 16] Most of AEDs either old generation or new generation are equally effective in treatment of epilepsy. However, the majority of drugs are prescribed symptomatically and target suppression of convulsions only, indifferent to disrupting the epileptogenic process by altering the signal changes responsible for seizures as well as decreasing the adverse effects of AEDs. [17]

The results of current study showed that there was lower incidence of seizures in epileptic children who were following BNF in comparison to children following regular practice. These findings are consistent with earlier studies of Zhuo C et al [18] as they recorded similar decrease in convulsion in epilepsy patients following titration of drugs by individualization.

Further, our study revealed adverse effects AEDs were significantly lesser in children following BNF compare to subjects following regular practice. These findings are very similar to the findings of previous studies of Sarkis et al [19] and Kanner AM et al. [20]

Sarkis et al [19] reviewed the potential impact of AEDs titration on cognition to improve the tolerability. Similar to the present study, Kanner AM et al [20] conducted a study regarding efficacy, safety, and tolerability of AEDs. They recorded that in order to improve safety and tolerability of some AEDs, requires slow and gradual dose titration.

In contrast to our study, Fishman J et al [21]claimed that low AEDs dose titration could result in suboptimal disease control and unexpected seizure breakthrough. However, their main concern was on healthcare resource use along with healthcare cost and they concluded that with titration the healthcare resource use rates, cost, and incidence of seizures increase.

These dissimilarities among the two groups which were observed in present study might be due to the group I who followed the regular practice was more likely to suffer from side effects of the medication as initiating or selecting the drug randomly with a maintenance dose or high dose without individualization of patients may not suite the patient age or epilepsy syndrome. [22] On the other hand, the group of patients who followed the BNF guideline experienced minimal adverse effect with seizure control and little dose adjustment needed in the population. This decrease of adverse effects might be due to individualization of patients

for the selection of suitable drugs as it can be helpful to achieve the minimum quantity of medicines to counter the seizure without or with minimal side effects. [23]

Treatment of epilepsy is started with the selection of the appropriate drug, its doses and titration; further, it should be strictly taken care of recommended process, age and requirement of the patients. Initial doses and titration rate are altered according to age, variety of seizures and drug type. [24] In addition, titration of an AED is a critical time during which the desire to quickly attain an effective dose must be balanced with the requirement to lessen side effects. Titration is possible if AED is selected on the basis of thorough history and individualization of patient. Initially, the AED regimen at lower doses and titrating the dose over period of weeks is often appropriate to minimize the potential side effect like: sedation, dizziness, blurred vision, attention problems, and headache or in coordination fatigue. But, more rapid titration is suitable for patient who suffers from recurrent seizures. [25]

Furthermore, an insignificant change in HQRL level of group II patients on BNF guidelines was observed compare to significant decrease in PedsQL score of group I patients in current study. These results are in accordance to the previous reports of Modi AC et al [26] and Jovanovic M et al [27] as they recorded significant effects of AEDs on PedsQL score of children suffering from epilepsy.

It has been shown in literature that various behavioral, educational, psychological and developmental disabilities found associated with long term consumptions of AEDs in pediatric population. [28] This study has proven that patients who were started on a small and slow dose titration as recommended by BNF guideline experience less adverse events while controlling their seizures. For almost 50 years, titrating of antiepileptic medications has been in use as a mean to enhance the efficacy and decrease the adverse effects of epilepsy treatment. [29]

New generation AEDs are more efficient in controlling the seizures compare to old generation AEDs; nevertheless, comparison of balance between benefits and adverse effects of both generations is still unclear. [30] Changes in behavior and cognitive functions are among mostly encountered side effects in patients especially children on AEDs. Moreover, these ill effects are difficult to distinguish in children as apparently parents are not able to differentiate alteration of behavior and cognitive functions. However, all these adverse effects could be resolve by modification or adjustments of AEDs. [31]

We have learned from history, and through individualization and the application of dose titration, that the use of AEDs implies significant variability especially in pediatric population, regarding dosing and adverse effect due to several changes in pharmacokinetic and pharmaco dynamics responses occur with maturation throughout childhood. [32]

Conclusion

The present study concluded that unbiased individualization of patients for the selection AEDs and its doses according to BNF guidelines has been found significantly effective in reducing the adverse effects as well as improved seizure control in pediatric population of India. Further, a large scale, multicenter efforts are needed to design, conduct a future clinically relevant randomized clinical trials that address the efficacy and tolerability of AEDs dose titration in pediatric population.

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