

# Brief Communication

## Patterns of antiepileptic drugs use in epileptic pediatric patients in Jordan

*Abla Albsoul-Younes, BSc, PhD, Lubna Gharaibeh, BSc, MSc, Amer A. Murtaja, BSc, MSc, Amira Masri, MD, Ibrahim Alabbadi, BSc, PhD, Abdelkarim A. Al-Qudab, MD.*

### ABSTRACT

**Objectives:** To determine prescribing patterns of antiepileptic drugs (AEDs) in pediatric patients with confirmed diagnosis of epilepsy, and to provide knowledge of general practice of physicians.

**Methods:** The study was a multi-center cross-sectional observational study, in specialized clinics for management of epilepsy in north, central and south Jordan. This study was conducted from January 2014 to July 2014. These were 3 from university tertiary care hospitals and 4 from governmental tertiary care hospitals.

**Results:** A total of 694 pediatric patients were included. Monotherapy AED use had the highest frequency 465 (67.0%), followed by dual therapy 162 (23.3%). The frequency of monotherapy in university hospitals was lower than governmental hospitals ( $p < 0.05$ ); however, Polytherapy was more frequent in younger children. Two old AEDs were most frequently prescribed as a monotherapy; Valproic acid 235 (50.5%) and carbamazepine 155 (33.3%). The most common combination in dual therapy was valproic acid with carbamazepine 28 (17.3%). The second most common combinations were carbamazepine with levetiracetam 21 (13.0%) or valproic acid with levetiracetam 20 (12.3%).

**Conclusion:** Older AED remain first line drugs for use in both monotherapy and combination therapy for epileptic disorders. Polytherapy is associated with younger kids and being treated in a university hospital.

Epilepsy is the most common neurological disorder in children. Successful management of epilepsy depends on many factors, including cause, type of

epilepsy, and antiepileptic drug (AED) selection. When an AED is chosen the following factors are important: dosing, compliance, side effects, monitoring, and pharmacokinetics.<sup>1,2</sup> The main goals of epilepsy therapy include complete seizure control, no adverse side effects, and optimal quality of life.<sup>3,4</sup> Drug therapy change and patients' noncompliance to treatment are a cited problem in patients with epilepsy.<sup>5</sup> The introduction of newer AEDs resulted in an increase in the potential for polytherapy regimens. However, sparse robust data support or refute polytherapy strategy. Moreover, physicians treating pediatric patients are challenged with scarce data that support their AED choice.<sup>6</sup> The aim of the current study was to determine prescribing patterns of AEDs in pediatric patients with confirmed diagnosis of epilepsy, and to provide greater knowledge of general practice in Jordan.

**Methods.** This study was a multi-center cross-sectional observational study. The centers included were from 2 educational tertiary-care hospitals (King Abdullah University Hospital and Jordan University Hospital), and 4 main governmental hospitals in north, central and south of Jordan. In the 2 educational hospital 3 clinics were included. An ethical approval to conduct the study was obtained from institutional review board committee in the 2 educational hospitals, as well as the ministry of health. The study was conducted between January 2014 and July 2014. Inclusion criteria were pediatric patients with the diagnosis of epilepsy, receiving at least one AED, and attending pediatric outpatients' clinics for general follow-up visits during study period. Guardian of eligible patient was asked for permission of enrolment of his child. After obtaining a signed consent from the child's legal guardians, a case report form was used to collect pertinent information. For the purpose of classification of AEDs in this study the following criteria was followed: AEDs in use before 1993 were considered old generation antiepileptic; including: phenobarbital, phenytoin, primidone, ethosuximide, carbamazepine, valproic acid, and clonazepam. Antiepileptic drugs in use after 1993 were considered new generation antiepileptic, these include: felbamate, gabapentin, lamotrigine, topiramate, tiagabine, levetiracetam, Oxcarbazepine, and zonisamide.<sup>7</sup> The data were analyzed using the Statistical Package for the Social Sciences (version 20, SPSS Inc., Chicago, IL, USA). Frequency and percentage were used to summarize categorical data (%), and quantitative data was described using the mean (mean  $\pm$ SD). Chi square was used to test for statistically significant difference in categorical data.

**Disclosure.** Authors have no conflict of interest, and the work was not supported or funded by any drug company. This study was funded by the Scientific Research Support Funds, Ministry of Higher Education and Scientific Research, Amman, Jordan (Grant No. MPH/1/02/2012).

doi: 10.17712/nsj.2016.3.20150766

Independent samples T test and one-way analysis of variance were used to test for statistical difference in continuous data. Multiple logistic regression was used to examine the effect of covariates or predictor variables. For all statistical test performed *p*-values less than 0.05 were considered statistically significant.

**Results.** A total of 717 pediatric patients with the diagnosis of epilepsy were screened for this study. Only 694 patients were included, 23 patients did not receive any AED at the time of inclusion in the study and were excluded. More than two thirds of participants were from the 2 educational hospitals 478 (68.9%) and the rest were from the governmental hospitals 216 (31.1%). The general information of the participants is included in Table 1. When governmental and educational hospitals were compared, there was no statistically significant difference concerning age (*p*>0.05). However, difference in gender was statistically significant among educational and governmental hospitals (*p*<0.05). The frequency of males was 63.9% in governmental hospitals compared to 52.3% in educational hospitals. The number of antiepileptic drug used in each patient ranged from monotherapy to more than 3 drugs. Monotherapy had the highest frequency 465 (67.0%), followed by dual therapy 162 (23.3%), triple therapy 52 (7.5%), and finally drug regimen that included more than 3 drugs 15 (2.2%). There was a statistically significant difference in the frequency of prescribing monotherapy between educational and governmental hospitals (*p*<0.05). The frequency of monotherapy in educational hospitals was 62.8% compared to 76.4% in governmental hospitals. The primary or initial AED prescribed to patients in monotherapy or combination therapy was mostly an old generation drug 607 (87.5%). The new generation drugs were the initial drug in 86 (12.4%) of patients, and one patient was prescribed vitamin B6 as the initial drug. The most frequently prescribed initial drug was valproic acid 329 (47.4%), it was followed by carbamazepine 209 (30.1%) (Table 2).

When comparing new or old generation drugs, the most frequently used drug as monotherapy was predominantly from the old generation of AEDs 410 (88.2%). Valproic acid was the most frequently prescribed AED (50.5% [n=235]) followed by carbamazepine (33.3% [n=155]). Dual therapy included several combinations of AEDs. The most common combination was valproic acid with carbamazepine (17.3% [n=28]), the second most common were 2 combinations namely: carbamazepine with levetiracetam (13.0% [n=21]) and valproic acid with levetiracetam (12.3% [n=20]). Other combinations used are shown in Table 3.

The combination between an old generation drug prescribed initially and a new generation drug prescribed as a second drug constituted 50% [n=82] of the dual therapy. There was a difference in the frequency of prescribing a new generation AED as an initial drug: it was 15.3% in educational hospitals versus 6.5% governmental hospitals. This difference was statistically significant (*p*<0.05). When a second AED was added to an old AED, this difference in choosing a new class drug for the second AED was reversed; 51.4% of second AED were new generation in educational hospitals compared to 66.7% in governmental hospitals. The effect of age, gender, and variation of hospitals (educational or governmental) on the likelihood of

**Table 1-** Participants' characteristics. n= 694

Variables	n (%)
<i>Gender</i>	
Male	388 (55.9)
Female	306 (44.1)
Age, years, mean ± SD	8.6±4.5
<i>Age groups</i>	
<1 year	28 (4.0)
1 to <6 years	229 (33.0)
6 years to <12 years	289 (41.6)
12 years to 18 years	148 (21.3)
<i>Distribution of patients by centers</i>	
Educational	478 (68.9)
Governmental	216 (31.1)

**Table 2 -** Frequency of initial therapy in monotherapy and combination therapy in 696 patients.

Monotherapy		Combination therapy	
Antiepileptic drug used	n (%)	Antiepileptic drug used	n (%)
Valproic acid	329 (47.4)	Lamotrigine	17 (2.4)
Carbamazepine	209 (30.1)	Oxcarbazepine	5 (0.7)
Phenobarbitone	50 (7.2)	Vigabatrin	4 (0.6)
Levetiracetam	30 (4.3)	Gabapentin	1 (0.1)
Topiramate	29 (4.2)	Phenytoin	1 (0.1)
Clonazepam	18 (2.6)	Vitamin B6	1 (0.1)

**Table 3** - Frequency of antiepileptic monotherapy and dual combinations.

Monotherapy n= 465	n (%)	Dual therapy combinations n=162	n (%)
Valproic acid	235 (50.5)	Valproic acid+Carbamazepine	28 (17.3)
Carbamazepine	155 (33.3)	Carbamazepine+Levetiracetam	21 (13)
Levetiracetam	19 (4.1)	Valproic acid+Levetiracetam	20 (12.3)
Phenobarbitone	17 (3.7)	Valproic acid+Topiramate	16 (9.9)
Topiramate	16 (3.4)	Valproic acid+Phenobarbitone	12 (7.4)
Lamotrigine	12 (2.6)	Valproic acid+Clonazepam	12 (7.4)
Oxcarbazepine	5 (1.1)	Valproic acid+Lamotrigine	9 (5.6)
Others	11 (1.3)	Others	44 (27.1)

participants receiving monotherapy or not was tested by using multiple logistic regression, the odds ratio was calculated for the covariates. Gender had no effect on the probability of receiving monotherapy or not. While age and whether educational or governmental hospital had a statistically significant effect on the likelihood of receiving monotherapy. As age of patients increased by one year the odds of receiving monotherapy was increased by 6.5% (odds ratio=1.065,  $p=0.001$ ), and patients in the governmental hospitals were more likely to receive monotherapy than those in the educational hospitals by 96.3% (odds ratio=1.963,  $p=0.001$ ).

When comparing new or old generation drugs, the most frequently used drug as monotherapy was predominantly from the old generation of AEDs 410 (88.2%). Valproic acid was the most frequently prescribed AED 235 (50.5%) followed by carbamazepine 155 (33.3%). Dual therapy included several combinations of AEDs. The most common combination was valproic acid with carbamazepine 28 (17.3%), the second most common were 2 combinations namely: carbamazepine with levetiracetam 21 (13.0%) and valproic acid with levetiracetam 20 (12.3%). Other combinations used are shown in Table 3.

**Discussion.** This study included only pediatric patients with confirmed diagnosis of epilepsy who had at least one drug. In agreement with published data the population of patients had slightly more males than females.<sup>8</sup> Moreover, the majority of patients (80%) were younger than 12 years of age. This is also in agreement with epidemiological study suggesting the incidence of epilepsy is more common in children younger than 12 years of age.<sup>8</sup> The percent of patients on monotherapy in this study is comparable to that reported for pediatric patients in a study from India,<sup>8</sup> but much higher than those reported from Italy and Oman.<sup>9,10</sup> However, our results are in disagreement with a recent study from India, reporting that carbamazepine was the

most commonly prescribed AED followed by valproic acid.<sup>8</sup> Valproic acid is AED that can be used for several types of epilepsy. A study from Saudi Arabia on epileptic patients 6 years or older with partial epilepsy with or without secondary generalization showed that 6 months treatment with valproate (sustained-release dosage form) as a monotherapy provided good seizure control and was well tolerated.<sup>11</sup> An interesting note is the fact that levetiracetam was the third most commonly used drug as monotherapy. In addition, it was frequently used in combinations. Levetiracetam has been reported to be the most frequently used AED in adults, but not in children.<sup>9</sup> The introduction of newer AEDs, increased the potential for poly-therapy regimens, although it seems more sensible to substitute rather than combine when the first AED is poorly tolerated, produces an idiosyncratic reaction, or shows no efficacy.<sup>6</sup> In the United Kingdom study rapid uptake of the newer AEDs in children was reported,<sup>12</sup> our study does not show high rate of new AEDs use. This might be due to the fact that clinicians are more conservative when treating younger children with newer AEDs compared to the adolescents; hence, the increase of newer AED prescribing is less significant when only investigating the younger age group of pediatrics (0-11 years).<sup>12</sup>

In conclusion, old generation AEDs are still the main treatment choice for children with epilepsy, the use of newer AEDs remains low. There is a considerable variation of newer AED use in children and adolescents among the countries, which may be attributable to different clinical guidelines and the healthcare systems within countries.<sup>13</sup>

*Received 12th November 2015. Accepted 9th March 2016.*

*From the Department of Biopharmaceutics and Clinical Pharmacy (Albsoul-Younes, Gharaibeh, Murtaja, Alabadi), Faculty of Pharmacy, Department of Pediatric (Masri, Al-Qudah), Faculty of Medicine, Hamdi Mango Center for Scientific Research (Albsoul-Younes), The University of Jordan, Amman, Jordan. Address correspondence and reprints request to: Dr. Abbla Albsoul-Younes, Department of Biopharmaceutics and Clinical Pharmacy, Faculty of Pharmacy, University of Jordan, E-mail: ablabsoul@yahoo.com / ablabsoul@ju.edu.jo*

**Acknowledgment.** *The author would like to thank the Scientific Research Support Funds, Ministry of Higher Education and Scientific Research, Amman, Jordan for supporting this study.*

## References

1. Sillanpaa M, Schmidt D. Predicting antiepileptic drug response in children with epilepsy. *Expert review of neurotherapeutics* 2011; 11: 877-885.
2. Hasan SS, Bahari MB, Babar ZU, Ganesan V. Antiepileptic drug utilisation and seizure outcome among paediatric patients in a Malaysian public hospital. *Singapore medical journal* 2010; 51: 21-27.
3. Tolaymat A, Nayak A, Geyer JD, Geyer SK, Carney PR. Diagnosis and management of childhood epilepsy. *Curr Probl Pediatr Adolesc Health Care* 2015; 45: 3-17.
4. Ohaeri JU, Awadalla AW, Farah AA. Quality of life in people with epilepsy and their family caregivers. An Arab experience using the short version of the World Health Organization quality of life instrument. *Saudi med J* 2009; 30: 1328-1335.
5. Cunnington MC, Webb DJ, Irizarry MC, Manjunath R. Risk factors for antiepileptic drug regimen change in patients with newly diagnosed epilepsy. *Epilepsy Behav* 2011; 21: 168-1672.
6. French JA, Kanner AM, Bautista J, Abou-Khalil B, Browne T, Harden CL, et al. Efficacy and tolerability of the new antiepileptic drugs, II: Treatment of refractory epilepsy: report of the TTA and QSS Subcommittees of the American Academy of Neurology and the American Epilepsy Society. *Epilepsia* 2004; 45: 410-423.
7. Sirven JI, Noe K, Hoerth M, Drazkowski J. Antiepileptic drugs 2012: recent advances and trends. *Mayo Clinic proceedings* 2012; 87: 879-889.
8. Mistry RA, Solanki KC, Prajapati HK, Doshi TM, Trivedi HR. Drug utilization pattern of antiseizure drugs and their adverse effects in the pediatric population, in a tertiary care hospital attached to a medical college. *Int J Basic Clin Pharmacol* 2014; 3: 336-342.
9. Malerba A, Ciampa C, De Fazio S, Fattore C, Frassine B, La Neve A, et al. Patterns of prescription of antiepileptic drugs in patients with refractory epilepsy at tertiary referral centres in Italy. *Epilepsy Res* 2010; 91: 273-282.
10. Al Za'abi M, Ahmed R, Al Asmi A, Al-Zakwani I. Utilization patterns of antiepileptic drugs among adult epileptic patients at a tertiary hospital in Oman. *Int J Pharm Pract* 2013; 21:117-122.
11. Deleu D, Al-Hail H, Mesraoua B, Mahmoud HA. Short-term efficacy and safety of valproate sustained-release formulation in newly diagnosed partial epilepsy VIPE-study. A multicenter observational open-label study. *Saudi med J* 2007; 28: 1402-1487.
12. Ackers R, Murray ML, Besag FM, Wong IC. Prioritizing children's medicines for research: a pharmaco-epidemiological study of antiepileptic drugs. *Br J Clin Pharmacol* 2007; 63: 689-697.
13. Hsia Y, Neubert A, Sturkenboom MC, Murray ML, Verhamme KM, Sen F, et al. Comparison of antiepileptic drug prescribing in children in three European countries. *Epilepsia* 2010; 51: 789-796.