

Antiepileptic drug utilisation and seizure outcome among paediatric patients in a Malaysian public hospital

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ABSTRACT

Introduction: The primary purpose of this study was to evaluate the utilisation pattern and seizure outcome of newer and older antiepileptic drugs in paediatric clinical practice in a Malaysian hospital setting.

Methods: Over a two-month period, all paediatric epilepsy patients from Penang General Hospital, Malaysia who were diagnosed according to the classification of the International League Against Epilepsy were followed up prospectively, and the patients' information was gathered with the help of a validated data collection form. This included demographic characteristics, monotherapy and polytherapy of antiepileptic drugs, as well as the number of seizures experienced.

Results: Partial seizures, including complex and simple partial seizures (47.2 percent), followed by generalised seizures (40 percent), were the most common seizure types found in this study. An average of 1.51 antiepileptic drugs per patient was prescribed, with 54.3 percent of the patients on monotherapy and 45.7 percent on polytherapy. Overall, sodium valproate was the most frequently prescribed antiepileptic drug (36.8 percent), followed by carbamazepine (30.2 percent) and lamotrigine (10.4 percent). Carbamazepine was the most frequently prescribed monotherapy (28.6 percent), followed by sodium valproate (17.1 percent). The newer antiepileptic drugs were also found to be used as monotherapy in 7.2 percent of the cases. Moreover, a significant difference was observed between the older and newer antiepileptic drugs in terms of the number of seizures experienced ($p = 0.027$). Most (75 percent) of the seizure-free patients were on carbamazepine monotherapy.

Conclusion: Monotherapy was the most frequently used remedy in all forms of epilepsy. Overall,

sodium valproate was the most commonly used drug, while carbamazepine was found to be more frequently used as monotherapy. There was a significant difference found between the older and newer antiepileptic drugs, with 87.5 percent of seizure-free patients on older antiepileptic drugs.

Keywords: antiepileptic drugs, benzodiazepine, drug utilisation, generalised seizure, partial seizure, monotherapy, polytherapy

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INTRODUCTION

Epilepsy is the most common neurological disorder in children, and it is characterised by a spontaneous propensity for recurrent and unprovoked seizures. Epilepsy, particularly childhood epilepsy, remains a challenge to treat. Despite the increase in the number of antiepileptic drugs (AEDs), more than 25% of children with childhood epilepsy continue to have seizures.⁽¹⁾ Around 4%–10% of children suffer at least one seizure in the first 16 years of life.⁽²⁾ The incidence is highest in children below 3 years of age, with a decreasing frequency in older children.⁽³⁾ Epidemiological studies reveal that approximately 150,000 children will sustain a first-time unprovoked seizure every year, and of those, 30,000 will develop epilepsy.⁽²⁾

The desired outcome of AED therapy is for patients to be seizure-free throughout the rest of their lives. However, the outcome of AED therapy in children depends on many factors, including selection, dosing and monitoring of AEDs, the identification of underlying cause, the type of seizures and the pharmacokinetic parameters of AEDs. All these factors are essential for successful management, but there is a lack of properly conducted outcome-based studies in paediatrics. The current AED development system essentially renders children with epilepsy “therapeutic orphans”, who can only benefit if the drugs developed for adults are also effective for children.⁽⁴⁾ Consequently, the clinical application and therapeutic use of AEDs are better

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Table I. Demographics of the epileptic patients (n = 70).

Demographic	No. (%)
Gender	
Male	44 (62.9)
Female	26 (37.1)
Total	70 (100)
Age (years)	
1–5	29 (41.4)
6–10	32 (45.7)
11–15	9 (12.9)
Total	70 (100)
Race	
Chinese	32 (45.7)
Malay	25 (35.7)
Indian	13 (18.6)
Total	70 (100)

recognised and established in adults than in children.

Different combinations of AEDs and monotherapy are used for the treatment of different forms of childhood epilepsy. Treatment should be aimed at controlling seizures associated with the lowest possible occurrence of adverse effects, thus allowing the child to become an active member of the community, and this, at the lowest possible overall cost. Data on the efficacy, potency, safety and tolerability of AEDs are critical in choosing the optimal AED, but monotherapy data specific to children is often not available. The ultimate outcome of AED treatment in paediatric epilepsy is to attain no seizures and no side effects. Fortunately, this goal is often met by using an appropriate AED as monotherapy.⁽⁵⁾

A previous hospital-based study, published in the year 2005, provided preliminary data on AED and its utilisation in 180 patients in the same hospital.⁽⁶⁾ Since then, no other epidemiological data on epilepsy has been generated from this country, highlighting the rationale for pharmacoepidemiological studies. In addition, no outcome-based studies in paediatrics have been conducted in Malaysia. A large majority of neurological patients are treated at tertiary referral centres in Malaysia. As all drugs prescribed in a government hospital are dispensed free of charge, the prescribing patterns for drugs can be evaluated with a high degree of accuracy. The aim of this study was to evaluate the drug utilisation pattern of AEDs prescribed for the treatment of various forms of epileptic seizures and to assess the outcome of AEDs in paediatrics.

METHODS

This was a cross-sectional, prospective study carried out over a two-month period, incorporating both descriptive and inferential analyses. The study was designed to evaluate the utilisation and outcome of AED therapy in

Table II. Patterns of AEDs prescribed.

Type of therapy	No. (%)
Monotherapy	38 (54.3)
Dual therapy	28 (40.0)
Triple therapy	4 (5.7)
Older AED	47 (67.1)
Newer AED	7 (10.0)
Older/Newer AED	16 (22.9)

AED: antiepileptic drug

children with epilepsy in a public hospital. All epileptic patients aged 1–15 years who were prescribed with at least one AED were included in the study. The patients were further classified into different age groups: 1–5, 6–10 and 11–15 years. Patients having seizures induced by drugs, or due to any trauma or disease were excluded from the study.

Convenience sampling was used to recruit all eligible patients in this study. Patients were identified through the neurologist and pharmacy drug prescriptions. The data collection form for this research was piloted on a sample of ten participants to ascertain the validity of the data collection forms. Participants who agreed to take part in the pilot were given a copy of the background information of the study, together with a consent form to read and sign before providing their comments. Participants were asked about their understanding of and comments on the form upon completing it. The feedbacks was then used to improvise the data collection form. A total of 109 patients were approached, of whom 70 agreed to participate in the study. The following data was retrieved from the prescriptions, medical records, attending doctors, nurses and family members: demographics, details of AEDs used, frequency of seizures and change in drug therapy during the study. The epileptic seizures were categorised according to the classifications of the International League Against Epilepsy.⁽⁷⁾ However, patients with more than one type of seizures were categorised as unclassified or a mixed type of seizure. The diagnosis was confirmed by a paediatric neurologist based on the clinical presentation of seizures, electroencephalography and scan tests. In addition, all the prescriptions were originated from the hospital paediatric neurologist.

Data collection was divided into two one-month periods. During the first month, demographic data was collected, and during the second month, epileptic patients were followed up on the number of seizures they experienced throughout the month and on any changes in their drug therapy. Information on the number of seizures experienced by patients attending the outpatient

Table III. Distribution of AED prescribed.

Type of AED	No. (%)
Most frequent dual combination (n = 28)	
Carbamazepine/Valproate	8 (11.4)
Valproate/Lamotrigine	6 (8.6)
Valproate/Phenytoin	6 (8.6)
Valproate/Topiramate	3 (4.3)
Others	5 (7.1)
Most frequent AED as monotherapy (n = 38)	
Carbamazepine	20 (28.6)
Valproate	12 (17.1)
Lamotrigine	3 (4.3)
Topiramate	2 (2.9)
Phenytoin	1 (1.4)
Overall AED utilisation (Total AED = 106)	
Valproate	39 (36.8)
Carbamazepine	32 (30.2)
Lamotrigine	11 (10.4)
Topiramate	8 (7.5)
Phenytoin	8 (7.5)
Levetiracetam	5 (4.7)
Vigabatrin	3 (2.9)

AED: antiepileptic drug

clinic was collected from the parents and other family members via telephone or email. However, first-hand information on the number of seizures experienced by patients in the ward was obtained from the attending doctors, nurses and family members on a daily basis. Depending on the number of seizures, the patients were categorised into Group A (no seizure), Group B (1–5/mth), Group C (6–10/mth) and Group D (> 10/mth). All follow-up patients were also classified into established (diagnosed with epilepsy for ≥ 30 days), recurrent (diagnosed with epilepsy after a remission period for > 6 months) and new-onset (diagnosed with epilepsy for < 30 days) cases.

The descriptive and inferential statistical analyses were carried out using the Statistical Package for Social Sciences version 13 (SPSS Inc, Chicago, IL, USA) for the analysis of the data at 0.05 level of significance. The Mann-Whitney test was applied to determine the difference in the number of seizures between sets of monotherapy and polytherapy, AED and AED/benzodiazepine (BZD). The Kruskal-Wallis test was applied to determine the differences among the older, newer and newer/older combination AEDs, as well as the established, recurrent and new-onset cases, which were further analysed by post-hoc Mann-Whitney test with Bonferroni's adjusted p-value to find the difference between the two groups (older and newer AED, older and older/newer AED, etc).

All the information was collected with the permission and approval of the Clinical Research Centre, the hospital director, and the research and ethics committee. All patients who agreed to take part

in the study were given a copy of the study background information together with a consent form. In addition, strict confidentiality was assured for the information collected.

RESULTS

A study cohort of 70 patients with a diagnosis of epilepsy and who were receiving at least one AED during the study period were included in the study. The demographic characteristics of the patients, including gender, age and race, are presented in Table I. 55 (78.6%) patients were treated as outpatients during the study period, and the remaining 15 (21.4%) patients were treated as inpatients. Of the 70 patients recruited, 32 (45.7%) patients were Chinese, 25 (35.7%) were Malays and 13 (18.6%) were Indians.

All the included patients in the study cohort were admitted to the hospital or had attended the outpatient clinic due to epilepsy. About 39% of the patients presented with complex partial seizures, followed by generalised tonic-clonic seizures (30.0%), infantile spasm (11.4%), simple partial seizures (8.6%), absence seizures (8.6%), and myoclonic and unclassified or mixed type seizures (1.4% each). Of the 70 patients, 46 (65.7%) were categorised under established cases, followed by recurrent (15, 21.4%) and new-onset cases (9, 12.9%).

The pattern of AEDs prescribed and the different therapeutic approaches of epilepsy treatment utilised are presented in Tables II and III. A total of 106 AEDs were prescribed to a total of 70 patients during the study period, which corresponded to an average of 1.51 AED per patient. In the group with seizures (complex and simple), 19 (27.1%) patients were on monotherapy, of whom 16 (84.2%) were on carbamazepine (CBZ) monotherapy. 11 (15.7%) patients were on a two-drug combination, of whom seven (63.6%) were using a combination of CBZ and sodium valproate (VPA). Only three (4.3%) patients were on a combination of three AEDs. In the group of patients with generalised seizures, such as tonic-clonic, absence and myoclonic seizures, 19 (27.1%) were on monotherapy, of whom 11 (57.9%) were on VPA, followed by CBZ (21.0%) and lamotrigine (LMT) (15.8%). Eight (11.4%) patients were on a combination of two AEDs, while only one (1.4%) was on a combination of three AEDs. Overall, only four (5.7%) out of 70 patients were on triple AED therapy; three from the partial seizure and one from the generalised seizure groups. All eight (11.4%) patients who were diagnosed with infantile spasm were on a combination of two AEDs.

Table IV. Number of seizures experienced by the patients per month (n = 49).

Variable	No. of patients	No. of seizures/mth (%)		
		1-5	6-10	> 10
Types of cases				
Established	46	12 (24.5%)	10 (20.4%)	7 (14.3%)
Recurrent	15	3 (6%)	2 (4.1%)	4 (8.2%)
New onset	9	6 (12.2%)	1 (2.1%)	4 (8.2%)
Classification				
Partial seizures	33	7 (14.3%)	9 (18.4%)	7 (14.3%)
Generalised	28	11 (22.4%)	3 (6%)	6 (12.2%)
Infantile spasm	8	2 (4.1%)	1 (2.1%)	2 (4.1%)
Unclassified	1	1 (2.1%)	0	0
AED and BZD combination				
AED only	33	11 (22.4%)	3 (6%)	6 (12.2%)
AED+BZD	37	10 (20.5%)	10 (20.5%)	9 (18.4%)
Type of AED and BZD combination				
BZD with 1 AED	25	9 (18.4%)	6 (12.2%)	4 (8.2%)
BZD with 2 AED	10	1 (2.1%)	4 (8.2%)	3 (6.1%)
BZD with 3 AED	2	0	0	2 (4.1%)
Type of treatment				
Monotherapy	38	12 (24.5%)	9 (18.4%)	5 (10.2%)
Polytherapy	32	9 (12.7%)	4 (5.7%)	10 (20.4%)
Type of AED				
Older	47	13 (26.5%)	11 (22.4%)	5 (10.2%)
Newer	7	4 (8.2%)	1 (2.1%)	2 (4.1%)
Older/Newer	16	4 (8.2%)	1 (2.1%)	8 (16.2%)

AED: antiepileptic drug; BZD: benzodiazepine

An increase in the AED dosage was noted in 18 (25.7%) patients, while the dose was maintained in the remaining 52 patients. 21 (30.0%) patients remained seizure-free during the follow-up period of the study, while 49 patients experienced a total of 422 seizures per month, with an average of 8.61 seizures per patient per month. The number of seizures experienced by the patients during the study period is presented in Table IV, while Table V shows the characteristics of patients who remained seizure-free throughout the follow-up period.

There was no significant difference ($p = 0.092$) in the established, recurrent and new-onset cases in terms of the number of seizures. However, there was a significant difference ($p = 0.027$) in the number of seizures in patients on older, newer and a combination of older/newer AEDs. The Bonferroni's adjusted p -value was calculated as 0.016, and based on that value, no difference was found between older and newer AEDs ($p = 0.712$), older and older + newer AEDs ($p = 0.018$), and newer and older + newer AEDs ($p = 0.092$). There was no difference found between monotherapy and polytherapy in terms of the number of seizures. Likewise, there was no difference ($p = 0.081$) in the number of seizures between AED alone and an AED/BZD combination.

DISCUSSION

This study described the utilisation and outcomes of

AEDs in a cohort of 70 patients observed and followed up in a tertiary care hospital for a duration of two months. The aim of AED therapy is to stop the occurrence or reduce the frequency of seizures with minimal adverse effects, and to improve the patients' quality of life. Unlike a previous study,⁽⁶⁾ the present study was a prospective, outcome-based pharmacoepidemiological study conducted in a Malaysian public hospital. In addition, most of the previous studies were carried out on adults with epilepsy,⁽⁸⁻¹²⁾ while the present study focused on children aged 1-15 years. Almost 87% of the patients were less than ten years old, with more than half of them in the 6-10 years age group. In keeping with earlier studies,^(6,9,13-16) epileptic seizures were found to be more common in male than female patients in the present study. However, the ethnic distribution of our study cohort contradicted a previous finding that epileptic seizures were more common in Malays than in Chinese.⁽⁶⁾

Most of the recurrent cases were found in the 6-10 years age group. Unlike the study by Ab Rahman et al,⁽⁶⁾ partial seizures followed by generalised seizures were the most common seizure type in our study, which was in line with the findings of Manford et al on adults,⁽¹⁷⁾ and Berg et al on children,⁽¹⁸⁾ where partial seizures were found to be the most common seizure type. The choice of AEDs depends on the proper classification of seizure type. In this study, CBZ was the most commonly used

Table V. Characteristics of seizure-free patients during the follow-up period (n = 21).

Variable	No. of seizure-free patients (%)
Type of cases	
Established	17 (81.0)
Recurrent	0 (0.0)
New onset	4 (19.0)
Classification	
Partial seizures	10 (47.6)
Generalised seizure	8 (38.1)
Infantile spasm	3 (14.3)
Unclassified	0 (0.0)
AED and BZD combination	
AED only	13 (61.9)
AED+BZD	8 (38.1)
Type of AED and BZD combination	
BZD with 1 AED	6 (28.6)
BZD with 2 AED	2 (9.5)
BZD with 3 AED	0 (0.0)
Type of Treatments	
Monotherapy	12 (57.1)
Polytherapy	9 (42.9)
Type of AED	
Older AED	18 (85.7)
Newer AED	0 (0.0)
Older/Newer AED	3 (14.3)

AED: antiepileptic drug; BZD: benzodiazepine

AED as monotherapy (84.2%) and as a combination of CBZ and VPA (50%) was most commonly used in partial seizures. VPA (57.9%), CBZ (21.0%) and, to a lesser extent, LMT (15%), were the AED of choice for generalised seizures. This is in line with the Malaysian Consensus Guidelines on the Management of Epilepsy 2005.⁽¹⁹⁾ Moreover, CBZ+VPA was the most commonly utilised combination in generalised seizures, followed by VPA+LMT. This study showed that the use of newer AEDs as monotherapy and polytherapy is likely on the rise. The increase in utilisation of newer AEDs has been attributed to the better side effects profiles reported for newer AEDs,⁽²⁰⁾ better awareness of the side effects of older AEDs, particularly in children,^(21,22) and the National Institute of Clinical Excellence's recommendation to use newer AEDs in children not benefitting from older AEDs or when the AEDs were unsuitable.⁽²³⁾ In the present study, a total of 106 AEDs were prescribed, with an average of 1.51 AEDs per patient, which was higher than in studies conducted in Oman (1.34)⁽⁸⁾ and Taiwan (1.41).⁽⁹⁾ VPA (36.8%) was the most commonly utilised AED, followed by CBZ (30.2%) and LMT (10.4%). CBZ (52.6%) was the most commonly utilised AED as monotherapy, followed by VPA (31.6%).

Monotherapy (54.3%) was the type of treatment most frequently utilised, which is consistent with a general estimate that 70% of childhood epilepsy can

Table VI. Comparison of antiepileptic drug pattern among Asian countries.

Country (year)	Total %			
	VPA	CBZ	PHE	PB
India (1999) ⁽¹⁶⁾	21	44	25	8
Taiwan (2000) ⁽⁹⁾	31	57	32	14
Oman (2002) ⁽⁸⁾	49	44	12	3
Malaysia (2005) ⁽⁶⁾	36.1	21.1	0	1.1
Present study (2010)	36.8	30.2	7.5	0

AED: antiepileptic drug; VPA: valproate CBZ: carbamazepine; PHE: phenytoin; PB: phenobarbitone

be controlled using monotherapy.⁽²¹⁾ Dual therapy was most frequently used in polytherapy. The present study showed that older AEDs (67.1%) were the most widely used for epilepsy treatment. A trend of prescribing newer AEDs as monotherapy was found in 13.2% of epileptic patients, whereas the use of older AEDs, such as phenytoin and phenobarbitone, was lower when compared to a previous study.⁽⁶⁾ Among the newer AEDs, LMT and topiramate were utilised as monotherapy. 74 (74%) patients continued with the same therapy, while in 26% of patients, an increase in dosage was noted during the follow-up period. Monotherapy was found to be the therapy of choice in the majority of epileptic patients, which was consistent with the findings of other studies.^(8,9,24,25) The AEDs were also utilised in combination with BZDs, such as clonazepam and nitrazepam, which are commonly used in adults as AEDs. The present study showed that more than half (52.9%) of the patients were on a AED+BZD therapy. The AED utilisation pattern in Asian countries is presented in Table VI. The studies included differ in design and age, but the objective was to compare and evaluate the use of AEDs in various countries. CBZ and VPA were the most widely used AEDs in these countries, accounting for over 20% of the prescriptions in monotherapy and polytherapy.^(6,8,9,16)

Controlling seizures with minimal adverse effects and maintaining the patient's ability to perform daily activities are the critical measures of treatment outcome. In this study, the outcome of the AED therapy was measured in terms of the number of seizures experienced by the patients throughout the follow-up period of one month. 21 patients remained seizure-free during that period, while 49 experienced an average of 8.61 seizures per month. In the group of partial and generalised seizures, 47.6% and 38.1% of patients were seizure-free, respectively. More patients from the group of AED without BZD (67.9%) were seizure-free compared to the AED+BZD group (38.1%). Among the AED+BZD group, 24% from the one AED+BZD group

and 9.5% from the two AED+BZD group were seizure-free, while no patient from the three AED+BZD group was seizure-free during the study period. Monotherapy was found to be superior to polytherapy in controlling seizures as 57.1% of the seizure-free patients were from this group as compared to 42.9% seizure free patients from the polytherapy group. Similarly, older AEDs were more effective in producing 85.7% seizure-free cases. It was also noted that no patient was seizure-free from the newer AED group, whereas 50% of patients in the combination of older/newer AED group experienced more than ten seizures per month. However, in most cases, BZDs, such as clonazepam, nitrazepam and other newer AEDs, were added when older or classical AEDs failed to suppress the seizures. Consequently, most patients on a AED+BZD combination were not seizure-free compared to those who were on AED without BZD in this study.

Based on the number of seizures experienced by the patients during the study period, 30.0% of the patients were each categorised into Group A (no seizure) and Group B (1–5 seizures/mth), while 18.6% of the patients were categorised into Group C (6–10 seizures/mth) and 21.4% into Group D (> 10 seizures/mth). This study attempted to identify the type of case, treatment, drug category or AED combinations that were more effective in controlling seizures in children. It was noted that there was no significant difference among the type of case (established, recurrent, new-onset) in terms of seizure control ($p = 0.092$), but 81% of the established epilepsy cases were seizure-free compared with the recurrent (0.0%) and new-onset (19.0%) cases. With regard to drug category (older, newer and their combinations), a significant difference was found among the drug categories in terms of the number of seizures ($p = 0.027$), as older AEDs were utilised more frequently in seizure-free patients (67.1%) than the newer AEDs (0.0%) and their combinations (32.9%). However, no significant difference was found between monotherapy and polytherapy ($p = 0.286$), although the majority of the seizure-free patients were from the monotherapy group. Similarly, there was no significant difference found between AED alone and AED+BZD ($p = 0.081$), which suggests that the addition of BZDs to the AED therapy did not improve the seizure profile of the patients in the present study. One possible explanation could be polytherapy, BZDs and newer AEDs were administered to the more refractory cases that were less likely to do well no matter what one did. Most of the seizure-free patients (75.0%) were on CBZ, and this finding indicates that CBZ was more effective as monotherapy than VPA.

However, the present study was not designed to make a comparison between the AEDs in terms of their efficacy as mono or polytherapy.

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