



ASSESSING THE PHARMACEUTICAL CARE ISSUES OF HOSPITALISED EPILEPTIC PATIENTS

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ABSTRACT

Studies concerning epilepsy in the context of Pharmaceutical Care in Malaysia are lacking. Thus, this study aims to determine the issues on hospitalised epileptic patients prescribed on anti-epileptic drugs (AED). Factors associated with uncontrolled seizure and hospitalisation and the drug related problems (DRP) encountered were described. Adult epileptic patients were screened and those fulfilling the inclusion criteria were recruited. These patients must be confirmed cases of epilepsy and on AED's for at least two months. The results showed 56.9% of patients' defaulted AED doses prior to the seizure attack. The remaining 43.1% of the patients were affected by emotional stress, fever, weather and alcohol. The DRPs identified were non-adherence towards medication (64.6%), dose inadequacy (51.9%), inappropriate drugs of choice with respect to specific indication (35%), underreporting of adverse effects (76.2%), underutilisation of Therapeutic Drug Monitoring services (41.5%) and inappropriateness of therapy of patients with liver diseases. Nevertheless, medication adherence was found to be the major factor for uncontrolled epilepsy (OR= 7.06, CI= 1.29-38.56, $P = 0.019$). Among the non-adherers, only 19% received medication counselling upon discharge ($P = 0.043$). In summary, pharmacists are needed to address the mentioned DRPs so as to optimize drug therapy in achieving the desired treatment goal.

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INTRODUCTION

Many epileptic patients might need to depend on antiepileptic medication for the rest of their lives (Vermeulen and Aldenkamp, 1995). Among those diagnosed with epilepsy, a vast majority are treated with AEDs and approximately 70% can become seizure free once the most effective regime is followed (Eatock, 2007). Recurrence and breakthrough seizure can be caused by variety of triggering factors. This can be related to both drug and non-drug related problems such as inadequate or suboptimal antiepileptic regimens, poor adherence, emotional stress and many others. AED therapy is also often associated with variety of adverse effects, and this might be the reason of non-adherence and poor quality of life of epileptic patients. Evidence suggests that adherence to medications among patients with epilepsy is sub-optimal (Briesacher, 2008; Davis, 2008; Ettinger, 2009). It is found that non-adherence to AEDs is associated with increased mortality, emergency department visits, hospitalisations, fractures, and head injuries (Davis, 2008; Ettinger, 2009; Faight, Duh, Weiner, Guerin, and Cunningham, 2008). Uncontrolled epilepsy in epileptic patients will give rise to seizure recurrence that leads to multiple admissions to hospitals. Ensuring the desired

clinical outcome is critical for these patients and the role of pharmacists in the healthcare team can benefit the overall management. This is because pharmacists have the knowledge and skill in recognizing DRPs and medication counselling that can further enhance the benefit of AED therapy. The main question is; do pharmacists have an important role in optimising the AED maintenance therapy in hospitalised epileptic patients. Thus the aim of this study is to describe the drug related problems in hospitalised epileptic patients. Objectively the study will identify the triggering factors that lead to hospital admissions due to breakthrough seizure, describe the drug related problems, identifying the factors associated with uncontrolled epilepsy and hospitalisation, and determining the areas where pharmacist's role is important in optimising antiepileptic drug therapy in epileptic patients.

MATERIALS AND METHODS

This is cross-sectional study where data were gathered from February to April 2010. Ethical approval was granted by the Research Ethics Committee of the Ministry of Health, Malaysia. Data were collected prospectively by convenient sampling method at the adult medical wards of a government hospital in Malaysia. This study focuses on patients with confirmed diagnosis of epilepsy and the drug related problems encountered during admission. All admissions due to seizure

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were screened and those fulfilling the inclusion criteria were recruited and followed until discharged. These patients must be between 18 – 65 years, with confirmed diagnosis of epilepsy, on AED's listed in the Ministry Of History formulary for at least two months. Absconded patients or those wished to be discharged at own risk was excluded. Patients that agreed to participate were asked to sign the consent form. Patients' information and details were transcribed on a Data Collection Form. These include past and present medications recorded at the emergency department and ward, year diagnosed, date of last admission, frequency of seizure, Therapeutic Drug Monitoring (TDM) assays results and relevant information from patients' medical records. The information written on the TDM reports were used to predict dose adequacy and adherence to AED prescribed. Dose adequacy is defined the serum level obtained is within the expected serum concentration of the patient's prescribed dose. These finding are then compared to the adherence status by estimating the expected value of the drug at steady state concentration. The assessment of adherence was carried out using Medication Adherence Report Scale (MARS) questionnaires. However, for patients deemed unfit to answer questions, a family member would be asked. MARS consists of five statements concerning self-reported adherence: forgetfulness, missing a dose, altering the dosage, stopping taking medication, and taking less than instructed. The statements have response categories on a five-point Likert scale and scores can range from 5 to 25, with higher scores indicating greater reported adherence. For each participant, a sum for MARS calculated ranging from 5 and 22 is as considered non-adherent while a score 23 or more as adherent. The patients were then categorised as being non-adherent and adherent in SPSS nominal data. Outcome measurement of the control of seizure is classified as good, partial and poor (Eriksson and Koivikko, 1997). Patient who is seizure free in one year is classified as good, partial if having one or more seizure during the last year, but no more than one per month while poor is patient having more than one seizure per month.

Data Analysis

Data were analysed using Statistical Package for Social Sciences (SPSS) version 17.0. The numerical scale data were tested for normality by using Shapiro Wilk test of normality. All other independent variables will be analysed using descriptive statistics. Chi-square tests with Yates continuity correction and Fisher's exact test were used wherever appropriate. For non-parametric data, Mann-Whitney's *U*-test and the Kruskal-Wallis test were used to measure for significance. A *P* value of < 0.05 was considered as being statistically significant.

RESULTS

The total number of admitted patients to the medical ward for seizure within the study period was 92 patients. Of these 19 patients were diagnosed for non-epileptic seizures, five absconded or requested to be discharged at own risk, four patients have no history of taking antiepileptic medications and six patients were being admitted twice within the study period. The final number of subjects who met the inclusion criteria was 65. The demographic characteristics of patients are

summarized in Table 1. Most were in the age range of 20-39 years. Majority were diagnosed as generalized epilepsy (89%) while one was diagnosed as absence seizure. Two patients had no epilepsy diagnosis were put under 'others' category. 8% were diagnosed as partial seizure. Figure 1 described the frequency of patients to number of diseases years. The result showed 38.5% of patients were in the category of 1- 5 years (38.5%). Patient's other concomitant diseases were assessed. 37% had one co-morbid and 23% of patients had more than one. The most common co-morbidities were psychiatric problems (13.8%), neurological problems (9.2%) and asthma and hypertension (7.7%) respectively. The common combinations of co-morbidities were asthma, hypertension and diabetes. 66.2% patients were in the partial control category, 21.5% were poorly controlled and eight patients had good seizure control.

Table 1. Patient demographics

Characteristics	Number of patients N (Percentage)
Age	
13-19	11 (16.9%)
20-39	32 (49.2%)
40-59	18 (27.7%)
60-79	4 (6.2%)
Total mean	33.4 ± 15.17
Gender	
Male	49 (75.4%)
Female	16 (24.6%)
Ethnicity	
Malay	18 (27.7%)
Chinese	9 (13.8%)
Indian	37 (56.9%)
Others	1 (1.5%)
Marital status	
Married	32 (49.2)
Single	32 (49.2)
Divorced	1 (1.5%)
Employment status	
Employed	27 (41.5%)
Unemployed	38 (58.5%)
Social History	
Smoker	15 (23.1%)
Non-smoker	38 (58.5%)
Alcoholic	12 (18.5%)
Family History of Epilepsy	
Yes	12 (18.5%)
No	53 (81.5%)

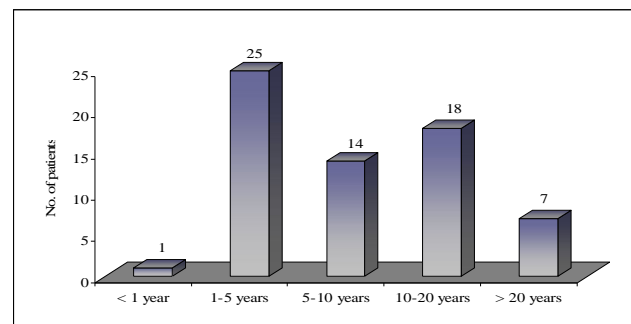


Figure 1. Years diagnosed with epilepsy

80% of the subjects had at least one hospital admission within the past one year while 20% had never been admitted before. However, the number of hospital admission was not normally

distributed (Figure 2). Figure 3 showed the reported seizure control of the patients included in the study.

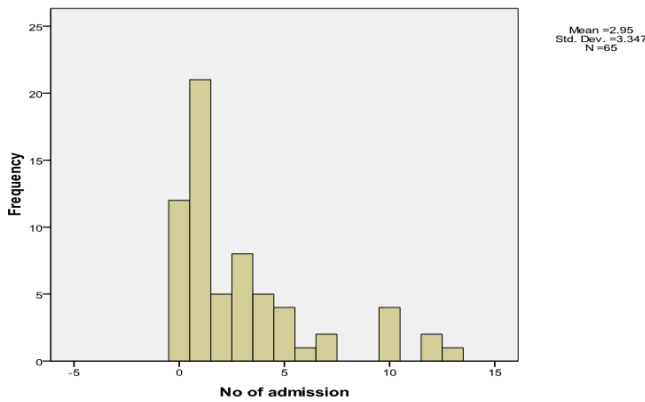


Figure 2. Number of admission within one year period

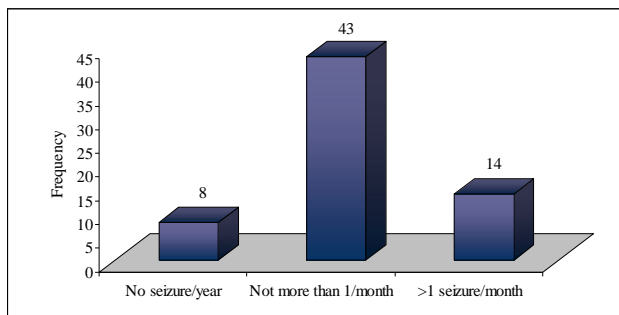


Figure 3. Reported seizure control

The triggering factors or reason of breakthrough seizures that lead to hospitalization were evaluated. 56.9% were non-compliant or defaulted treatment. 26.2% claimed having altered physiological changes such as fever, stress or emotional disturbances and one reported an episode of cerebro-vascular accident. The external factors (16.9%) were contributed by weather and alcohol intoxication. (figure 4)

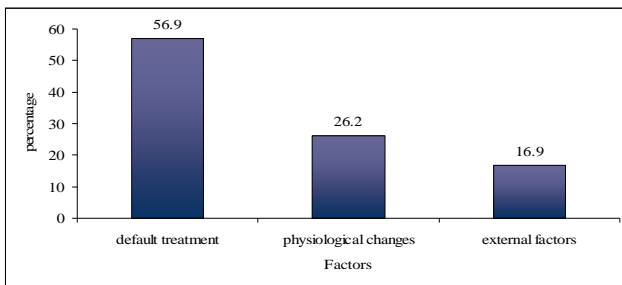


Figure 4. Factors identified for breakthrough seizure

12 patients claimed being prescribed with drug (s) to control their seizure (Table 2). For those with known AED therapy, sodium valproate was the most prescribed monotherapy (36.9%), phenytoin (13.8%) and the combination of sodium valproate with phenytoin (12.3%). Patients prescribed with phenytoin monotherapy were diagnosed as generalised seizures. Only one partial seizure patient had a combination

therapy of sodium valproate and phenytoin while the rest were for generalised seizures. Of the combination therapy, sodium valproate and phenytoin combination is the most prescribed (26.9%)

Table 2. AED Maintenance Therapy in regards to the Type of Epilepsy

AED Therapy	Type of Epilepsy	
	Generalised Seizure	Partial seizure
Monotherapy		
Sodium Valproate (VPA)	22	2
Phenytoin (PHT)	9	0
Polytherapy		
VPA + PHT	7	1
VPA + CBZ	3	0
VPA + Lamotrigine	3	0
VPA + Phenobarbitone	1	0
CBZ + Lamotrigine	1	0
VPA + PHT + Lamotrigine	1	0
VPA + CBZ + Levetiracetam	1	0
Unknown AED	10	2

The daily of prescribed dose was evaluated and inadequate dose group (50.8%) outnumbered the adequate dose group (49.2%). Even though the difference is insignificant, the adequacy of dose can be considered as one of the important factors of hospitalization. Medication adherence assessment was summarized in Figure 6. 64.6% of the patients have a certain degree of non adherence to the prescribed medication whereas the remaining 35.4% of patients were adherent to their medication.

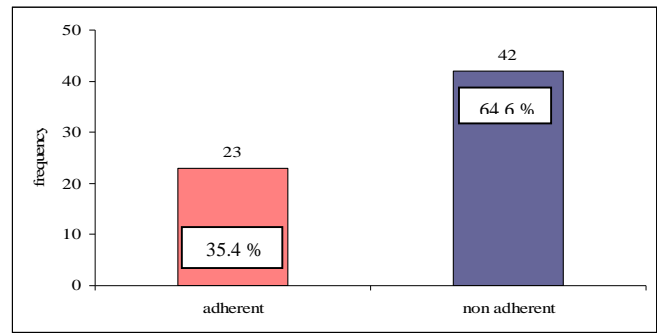


Figure 5. Patients adherence towards prescribed AED.

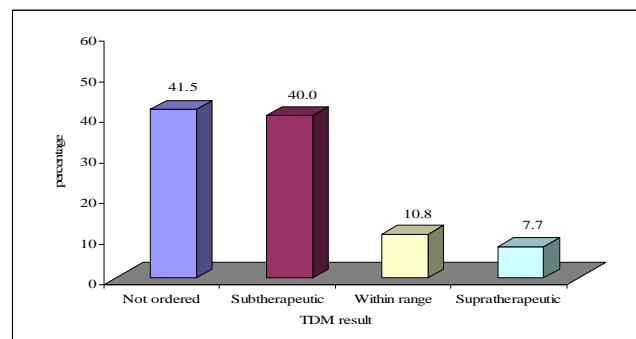


Figure 6. The results of TDM requests

TDM records showed that 41.5% of the subjects had never had any AED drug levels monitored. Of those who had their AED drugs levels monitored, 40.0% were subtherapeutic, 10.8% in

normal therapeutic range and 7.7% were higher than the normal range (Figure 6). The records also found that a large number of patients not being assessed for any adverse drug effects due to medication. Thirty-one percent of patients claimed one or more side effects such as drowsiness and headache (80%). However, only 5% of the cases were being documented. Gingival hyperplasia was observed in one patient during the study period. 32.3% cases have normal values and 47.6% had abnormal values for liver function tests. For cases with abnormal values, 30.8% had one high value and 13.8% had more than one tests higher than normal range. 13% of the patient did not have LFT investigation during the period of stay in the hospital.

Table 3. Results of Liver Function Test parameters

LFT values	Frequency (n)	Percent (%)
all normal	21	32.3
≥ 1 low	2	3.1
≥ 1 high	29	44.6
not tested	13	20.0
Total	65	100.0

Chi-Square test was performed to evaluate the relationship of medication adherence with seizure control. Results showed that non-adherent patients tend to have more uncontrolled seizures than adherent patients (0.02). The Odds Ratio (7.06) value showed a substantial probability of having seizure if the patient does not adhere to their medication with confidence interval of 1.29-38.56.

Table 4. Association of non-adherence and seizure outcome

Outcome	Odds Ratio	95% Confidence Interval		P value
		Lower	Upper	
Partial/poorly controlled seizures	7.059	1.292	38.56	0.019 *
History of hospitalisation	1.765	0.513	6.067	0.518

* statistically significant (P<0.05)

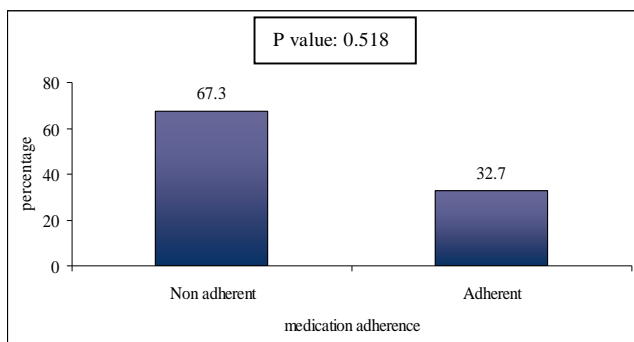


Figure 7. Adherence status among patients who have had history of hospitalisation

An evaluation to show the importance of medication adherence to epileptic patients was undertaken. This is done by correlating between history of hospitalization for the past one year (nominal data) with adherence but the correlations are insignificant. Nevertheless, figure 8 showed that patients with a history of at least one hospitalization within the period of one

year due to breakthrough seizure were mainly non-adherers (67.3%). The adequacy of dosage of prescribed medication against patients' seizure frequency showed no significant relationship. However, cross tabulation between history of hospitalization and dose adequacy showed 59.1% of all cases with history of at least one admission for the past one year have inadequate AED doses.

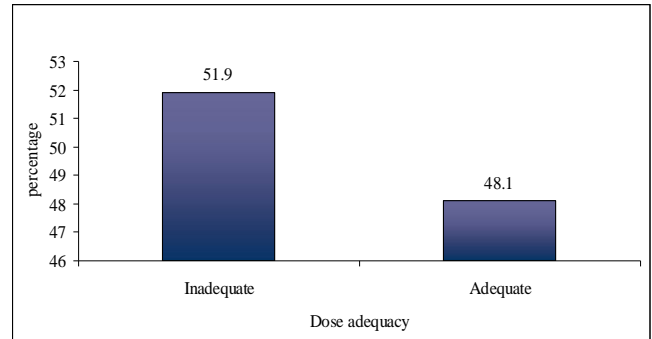


Figure 8. Adequacy of the dose prescribed among patients with hospitalisation history

The association of drug adherence and TDM found that 73.1% of non-adherent cases had sub-therapeutic AED level. However, 60% of adherent patients had levels within therapeutic and supra-therapeutic range while the non-adherers had 42.8%. 57.7% in the dose adequacy group had subtherapeutic blood levels. These findings showed that AED monitoring is important to predict medication adherence and dose adequacy in epileptic patients (Figure 9 and 10)

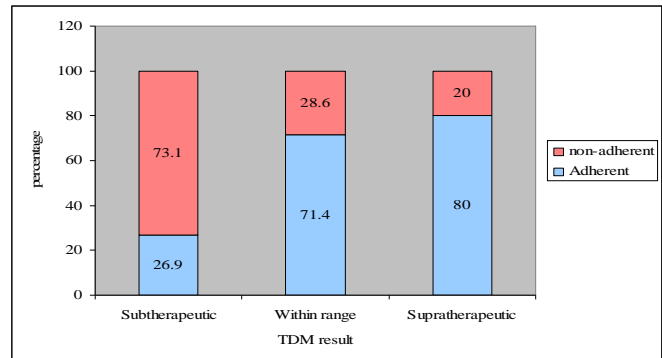


Figure 9. Association of TDM results with adherence status

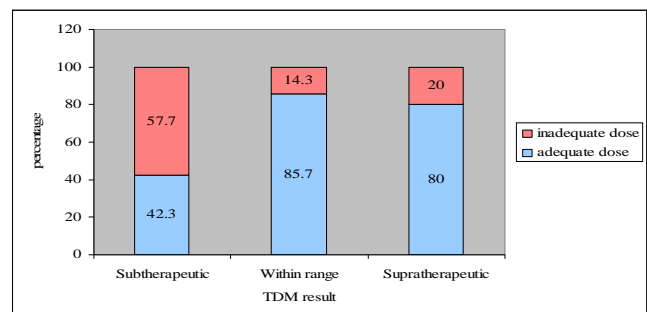


Figure 10. Association between TDM results and dose adequacy

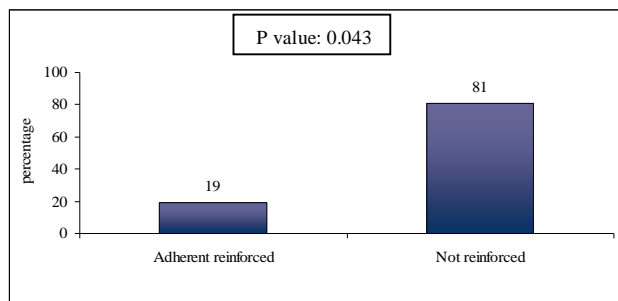


Figure 11. Adherence reinforcement among non-adherent patients upon discharge

The findings also found two patients diagnosed with liver cirrhosis and Hepatitis C but were being prescribed with sodium valproate. The Hepatitis C patient had a significant increase in ALP, ALT and bilirubin values, whereas the liver cirrhosis patient had LFT parameters at the upper end of the normal values. In addition, there were two alcoholic patients being prescribed with sodium valproate whereby caution should be considered. Finally, Figure 11 showed the number of medication reinforcement counselling prior discharge for non-adherent patients. Only 19% received education ($p=0.04$) and this is a critical part in the therapy management which have been overlook.

DISCUSSION

The majority of patients in this study falls under the age group of 20-39 years old is in line with the Malaysian Population Census, 2009 and similar to that reported by Banerjee, Filippi and Hauser (2009). 75.4% of the study population were male patients and is similar to earlier reports (Barucha *et al.* 1998, Hauser, 1999; Mac *et al.*, 2007; Banerjee *et al.* 2009, Amatniek, Sorra, Frey, and Hauser, 2010). Manjunath *et al.* (2009) also mentioned that males are more inclined to incur certain types of seizure aetiologies; e.g., traumatic brain injury which may explain the statistic observed. There are several non-drug related problems identified in this study. Family history is a non-DRP issue that contributed to about 18.5% of patients family history of epilepsy. This finding was mentioned by Hauser (1999) where familial aggregation for epilepsy is consistent with both common environmental exposures as well as genetic tendency for the disease. Most patients were diagnosed as having generalised seizures and others had reported similar findings (Loh, Lee, Yew and Tjia, 1999 and Aldenkamp and Van Donselaar, 2003). The current findings is also observed by a local study conducted in 1993 on 593 Kelantan patients where 53.1% of patients had generalised epilepsy and 16.7% had partial epilepsy. The most common concomittant disease found in this study was psychiatric problems (13.8%) and neurological disorder (9.2%). It is similarly reported by Shyam Babu, Satishchandra, Sinha, and Subbakrishna (2009), where they mentioned that mood disorders are an important problem among patients with epilepsy. Boro and Haut (2003) nevertheless had earlier stated that mood disorders, predominantly major depression, and anxiety disorders have the highest frequency, followed by psychosis. The triggering factors of an epileptic seizure attack were examined. This study found omitting of AED doses prior

to admission was the most common triggering factor. Other triggering factors were physiological/emotional changes before admission, stress or emotionally disturbed. This finding is consistent with other studies (Pinikahana and Dono, 2009; Nakken *et al.*, 2005; Tan *et al.*, 2005) which reported that emotional stress contributes vastly to the occurrence of seizures. Omission of AED is a drug related problems that pharmacist should take action since the findings showed 64.6% were non-adherent. This finding is consistent with many other studies that investigate the magnitude of adherence among patients with epilepsy (Brown, Sheeran and Reuber, 2009; Ettinger *et al.*, 2009; Jones *et al.*, 2006; Cramer *et al.*, 2002). Non-adherence can be link with poorly controlled epilepsy, more hospital admissions and emergency room visits, increase in total health care cost (Ettinger *et al.*, 2009) and decrease in patients' overall quality of life (Hovinga *et al.*, 2008).

Appropriate and effective AED therapy is critical to ensure optimal seizure control. A report by Chadwick (1987) examined the therapeutic potential of monotherapy and confirmed that a single drug can be as effective, and in some cases more effective, than polypharmacy. The relevance of monotherapy is supported by Richardson *et al.* (2004) on seizure control and quality of life of medically refractory epilepsy patients converted from polypharmacy to monotherapy. Their findings showed none of the 35 patients had worsening of their seizure frequency after conversion to monotherapy was completed and 80% had a 50% or greater reduction with conversion to monotherapy and maintained that reduction for at least 12 months. This study substantiates that prescribing more than one drug can be one of the pharmaceutical care concerns as it can reduce patients adherence, increase risk of adverse effect and drug interaction and increase the unnecessary cost of treatment. Most of the commonly prescribed AEDs have narrow therapeutic index and non-adherence will render the drugs to be in subtherapeutic concentration (McAuley *et al.*, 2008), hence making the therapy suboptimal. This is rather obvious since 60% of studied patients had poor control. However, Schmidt (2009), reported that the treatment of patients with uncontrolled epilepsy with suboptimal doses may prevent seizure remission and could be the reason for 40% had good seizure control. TDM is an issue that must be taken seriously so as to ensure compliance and prevention of adverse drug effects for AEDs (Johannessen, 2004, Patsalos *et al.* (2008). The low number of TDM request and acceptance of recommendation found in this study is an indication that pharmacist should upgrade their knowledge in the pharmacokinetic and pharmacodynamic properties of AEDs. This association is important in overcoming the DRP issues of poor knowledge and adherence to medication.

Side-effects or adverse drug effects are DRP issues can lead to poor adherence. Pharmacist can determine the presence of side-effects or adverse effects by employing the checklist method by Carreno *et al.* (2008). The method found that 65.2% of the patients reported having adverse effects when administered a list of possible side effects while 33.7% reported adverse effects spontaneously. Without the checklist, patients might not be aware that a particular discomfort is an adverse effect of the drug, and that the problem is medication-related. The inappropriate prescribing of AEDs on patients with liver disease, liver cirrhosis and Hepatitis C respectively, and

chronic alcoholics is rather controversial and can be a serious DRP issue (Ahmed and Siddiqi 2006, Asconape, Penry and Dreyfuss, 1993, British National Formulary 2010). Again the relevance of pharmacist involvement in the management of AEDs is crucial. The importance of pharmacist intervention is proven by Kanjanasilp *et al.* (2008). In the study, seizure-frequency group is a clinical outcome and prior to providing the pharmaceutical care, the abovementioned researchers identified the most frequent seizure-frequency groups, i.e. seizure-free (46.15%) and high frequency (28.85%). In the period after provision of pharmaceutical care, the most frequent seizure frequency groups were seizure-free (71.15%), and high frequency (13.46%). These results indicate that the majority of patients could control their seizures after the pharmacist had provided pharmaceutical care.

Conclusion

This study found the reasons for hospital admission due to seizures can be both drug and non-drug related. The drug related problems are mainly being non-adherent, inappropriate drug and dose, side-effects or adverse drugs, lack of education on disease and drugs, inadequate TDM and inappropriate prescribing of AEDs for patients with liver diseases. Non-drug related problems include emotional stress, physiological changes and external factors. To address the drug related problem, pharmacist should be involve in both pharmacological and the non-pharmacological management of seizures. Patients can be given counselling on how to deal with emotional disturbances due to drugs. Additionally, there is a critical need of continuous assessment of patient's understanding on the disease and drug related problems. Follow up reinforcement of adherence must also be practice. However, due to the study design and the low sample size, the observed findings might be bias and generalizability to other populations can be questionable. However this study has able to highlight the issues concerning pharmaceutical care and the role of pharmacist.

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