DETERMINATION OF VALPROIC ACID REFERENCE RANGE AND PREDICTORS FOR GOOD SEIZURE CONTROL AMONG PATIENTS WITH EPILEPSY AT HOSPITAL KUALA LUMPUR

by

MASTURA BINTI AHMAD

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AAN	American Academy of Neurology
AES	American Epilepsy Society
AEDs	Anti-epileptic drugs
AUROC	Area Under Receiver Operating Curve
BMI	Body mass index
CAE	Childhood absence epilepsy
CI	Confidence interval
CNS	Central nervous system
CT-scan	Computed tomography scan
EEG	Electroencephalogram
HR	Hazard ratio
IGE	Idiopathic generalized epilepsy
ILAE	International League Against Epilepsy
JME	Juvenile myoclonic epilepsy
GTCs	Generalized tonic-clonic seizure
LAMIC	Low- and middle- income countries
MRI	Magnetic resonance imaging
NICE	National Institute of Clinical Excellence
OR	Odds ratio
PTE	Post-Traumatic Epilepsy
PTSD	Post-traumatic seizure disorder

QOL	Quality of life
RR	Relative risk
SDC	Serum drug concentration
SE	Status epilepticus
SIGN	Scottish Intercollegiate Guidelines Network
SUDEP	Sudden Unexplained/Unexpected Death in Epilepsy
TDM	Therapeutic Drug Monitoring

PENENTUAN JULAT RUJUKAN ASID VALPROIK DAN PERAMAL-PERAMAL KAWALAN SAWAN DI KALANGAN PESAKIT-PESAKIT EPILEPSI DI HOSPITAL KUALA LUMPUR

ABSTRAK

Asid valproik, ubat sawan berspektrum luas, telah dibuktikan berkesan dan mempunyai kesan sampingan yang rendah, tetapi kepentingan pemantauan kepekatannya dalam darah didapati kurang jelas. Kajian ini dijalankan untuk menentukan julat kepekatan berkaitan dengan keberkesanan dan kesan sampingan asid valproik dan faktor-faktor yang menentukan penyakit sawan dapat dikawal. Satu kajian pemerhatian secara retrospektif kohort telah dijalankan ke atas pesakit-pesakit yang menerima rawatan asid valproik di Klinik Neurologi, Hospital Kuala Lumpur. Kumpulan 'respons baik' terdiri daripada pesakit-pesakit yang memperolehi 50% atau lebih penurunan kekerapan sawan. Kumpulan 'respons lemah' terdiri daripada pesakit-pesakit yang tidak mencapai 'respons baik'. Kekerapan sawan dikira dari rekod perubatan, catatan harian pesakit dan disahkan dari buku catatan yang dibekalkan semasa kajian. Pensampelan darah untuk menentukan kepekatan asid valproik dijalankan pada temujanji pertama dan pada bila-bila masa sepanjang tempoh kajian. Buku catatan harian yang dibekalkan semasa kajian bertujuan untuk meningkatkan tahap kepatuhan terhadap ubat dan merekod kesan-kesan sampingan yang dialami. Seramai 242 pesakit menyertai kajian ini mulai Januari 2011 dan diikuti selama setahun. Seramai 76 orang pesakit dari kumpulan 'respons baik' dan bersetuju kepekatan darahnya dipantau digunakan untuk penentuan julat rujukan. Beberapa pendekatan diambil untuk menghasilkan julat rujukan, (i) menggunakan purata

atau median kepekatan, (ii) melalui julat kepekatan di mana peningkatan respons pesakit berlaku secara mendadak dengan meningkatnya kepekatan asid valproik, (iii) melalui julat komposit yang ditentukan secara mudah berdasarkan (i) dan (ii) untuk menghasilkan julat di mana kebanyakan pesakit mendapat 'respons baik' dengan kesan sampingan yang minima. Jika lebih dari satu julat dihasilkan, julat-julat tersebut dianalisa secara statistik untuk mendapatkan julat yang paling sesuai. Julat rujukan yang ditunjukkan oleh kumpulan pesakit ini ialah 40 hingga 85mg/L. Kesan sampingan menggeletar dikaitkan dengan kepekatan asid valproik melebihi 80mg/L dan kehadiran kesan sampingan lain. Faktor penentu yang mengaitkan kesan rawatan yang baik untuk pesakit-pesakit sawan dengan asid valproik ialah umur semasa rawatan ubat sawan dimulakan [nisbah odd terselaras 0.96, 95% selang keyakinan (0.920, 0.995), P=0.027], rawatan dengan asid valproik sahaja [nisbah odd terselaras 4.74, 95% selang keyakinan (2.258, 9.947), P<0.001], keputusan imbasan MRI/CT yang normal [nisbah odd terselaras 5.83, 95% selang keyakinan (2.507, 13.552), P<0.001], tidak merokok [nisbah odd terselaras 3.23, 95% selang keyakinan (1.099, 9.473), P=0.033], dan ketiadaan tekanan [nisbah odd terselaras 19.98, 95% selang keyakinan (9.255, 42.764), P<0.001]. Kajian ini menunjukkan julat rujukan asid valproik untuk populasi ini dan faktor-faktor penting yang menentukan kesan rawatan yang baik untuk pesakit-pesakit sawan yang menggunakan asid valproik.

DETERMINATION OF VALPROIC ACID REFERENCE RANGE AND PREDICTORS FOR SEIZURE CONTROL AMONG PATIENTS WITH EPILEPSY AT HOSPITAL KUALA LUMPUR

ABSTRACT

Valproic acid, a broad spectrum anti-epileptic drug, had been proven efficacious and tolerable, but its serum drug concentration monitoring value remains obscure. This study was carried out to determine valproic acid concentration range associated with efficacy and tolerability, and the prognostic factors associated with seizure control. A retrospective cohort, observational study was conducted in patients who received valproic acid treatment in Neurology Clinic, Hospital Kuala Lumpur. 'Good response' group were patients experiencing 50% or more seizure reductions. 'Poor response' group were patients who did not achieve the definition of 'good response'. Seizure frequency was assessed from medical record, patients' own diary and verified by seizure diary supplied during this study. Blood sampling for determination of valproic acid concentration was done on the first encounter with the patient and/or at any time during the study period. Seizure diary was used as a tool to improve patient's adherence and record side effects occurrence. A total of 242 patients were recruited from January 2011 and followed up for a year. Seventy-six patients with 'good response' and consented to serum concentration monitoring were included for reference range determination. Several approaches were exercised to generate reference ranges, (i) mean or median concentration, (ii) range associated with a sudden increase in response with increasing valproic acid concentration, (iii) a composite concentration range based on (i) and (ii)

determined arbitrarily to produce majority of patients with ‘good response’ and minimal side effects. When more than one concentration ranges of potential exists, they were tabulated and statistically analyzed to find the most acceptable concentration range. The reference range provided by this population is 40 to 85mg/L. Tremor was associated with valproic acid serum concentration above 80mg/L and the presence of other side effects. Significant prognostic factors associated with good seizure response in patients with epilepsy on valproic acid were age at the initiation of AED [Adjusted OR 0.96, 95% CI (0.920, 0.995), P=0.027], on valproic acid monotherapy [Adjusted OR 4.74, 95% CI (2.258, 9.947), P<0.001], normal MRI/CT-scan [Adjusted OR 5.83, 95% CI (2.507, 13.552), P<0.001], non-smoking [Adjusted OR 3.23, 95% CI (1.099, 9.473) P=0.033] and absence of stress [Adjusted OR 19.98, 95% CI (9.255, 42.764), P<0.001]. This study described valproic acid reference range for this population and highlighted the important prognostic factors that were associated with favorable seizure response in patients with epilepsy on valproic acid.

CHAPTER ONE

INTRODUCTION

1.1 Disease Burden

Epilepsy is associated with high morbidity and mortality which ultimately affect the country's economic burden and patients' socioeconomic status. Epilepsy-related negative outcomes incur high direct healthcare cost and indirect cost. Indirect cost relates to qualitative and quantitative loss of productivity, income and social well-being.

1.1.1 Impact on Morbidity and Quality of Life

Although epilepsy takes place in the brain, it profoundly influences the morale, wellbeing, self-image and lifestyle of patients (Betts 1992). It has negative impact on patient's quality of life, which was worsen by the adverse effects of antiepileptic treatments (Rogvi-Hansen & Gram 1995, Yue et al. 2011). It is also associated with psychiatric morbidity (Dias et al. 2010).

A large scale Quality Of Life (QOL) study in more than 5,000 patients with epilepsy in 15 European countries by Baker et al. (1997) has shown negative impact of epilepsy on social and psychological well-being. Significant reductions were found in physical, social and emotional functioning. A similar study in the United Kingdom by Moran et

al. (2004) confirmed the negative impact of epilepsy. It causes work and school difficulties and driving prohibitions as well as affecting psychological and social life. Loss of seizure control leads to missed school or a permanent drop from school or work as a result of cognitive impairment in 38% of the patients and perceived stigma in 31% (Hovinga et al. 2008).

Depression is common in patients with epilepsy (Roth et al. 1994, Hecimovic et al. 2003, Kanner 2007, Ekinci et al. 2009, Dias et al. 2010). It occurs more often in patients whose seizure is not in remittance (Jacoby et al. 1996) and those who lead stressful life events (Roth et al. 1994). In addition, young patients with epilepsy reported increased anxiety and more emotional and behavioral difficulties (Ekinci et al 2009, Eddy et al. 2010). Psychiatric comorbidities, lack of seizure control, motor impairment and cognitive impairment also contribute to various physical injuries (Wirrell 2006).

Physical injuries lead to frequent physician visits, hospitalizations and reduced productivity from missing schools and works (Begley et al. 1999, Wirrell 2006, Davis et al. 2008, Hovinga et al. 2008). In patients with epilepsy, there is an increased likelihood of hospitalizations and motor-vehicle accidents due to seizure compared to other population (Hovinga et al. 2008). There is a two-fold increase in risk of fractures, either as a direct effect of seizure-induced injury or due to drug-induced reduction in mineral bone density (Wirrell 2006).

In a study by Persson et al. (2002), 11% of 177 patients with epilepsy sustained 23 fractures which prompted them to seek medical attention at the emergency department. This study compared the incidence of extremity fractures in adult patients with epilepsy with the incidence of fractures in the general population in the same geographic area. They found that the relative risk of fractures was higher during the first and second year compared with more than 5 years after diagnosis (RR, 3.71; 95% CI, 1.20–11.48). Male aged 45 years or older and those with generalized seizures were particularly at risk. This finding was supported by Kwon et al. (2010). The 1-year incidence of one or more injuries was significant among persons with epilepsy (20.6%) compared to those without epilepsy (16.1%, $p < 0.001$). Of the 16 types of injuries studied, 11 were higher in persons with epilepsy compared to those without epilepsy, which included head and skull fractures (OR = 2.6, 95% CI 1.6–4.2), neck/thoracic/trunk fracture (OR = 2.2, 95% CI 1.6–3.2), upper limb fracture (OR = 1.3, 95% CI 1.0–1.6) and lower limb fracture (OR = 1.8, 95% CI 1.4–2.3). Other injuries reported were upper limb dislocation (OR = 1.4, 95% CI 1.0–2.1), neck/thoracic/trunk crushing injury (OR = 1.1, 95% CI 1.0–1.3), upper limb crushing injury (OR = 1.3, 95% CI 1.2–1.5), lower limb crushing injury (OR = 1.3, 95% CI 1.1–1.5), intracranial injury (OR = 1.7, 95% CI 1.3–2.3), other head injury (OR = 2.2, 95% CI 1.9–2.5), and multiple injuries (OR = 1.6, 95% CI 1.1–2.5).

Long-term antiepileptic drugs have been significantly associated with the acceleration of atherosclerosis in patients with epilepsy (Tan et al. 2009). Chronic exposure to AEDs may alter the oxidative/antioxidative balance that results in oxidative stress which further damages endothelial cells (via increase in carotid intima media thickness) and contributes to the atherosclerotic process (Hamed et al. 2007). To my knowledge, there

is no data on increase acute coronary syndrome among patients with epilepsy. Currently available research showed increased in atherosclerosis biomarkers in patients with AEDs. Hamed et al. (2007) provided the first report on the high vulnerability of developing atherosclerosis among patients with epilepsy. Approximately 50% of patients with epilepsy developed thickened carotid artery. Carbamazepine and valproic acid showed significant alterations in certain atherosclerosis biomarkers.

1.1.2 Impact on Mortality

Patients with epilepsy have a higher risk of incurring accidental injury than those without seizure, which may also lead to death. Seizures may lead to abrupt falls consequently leading to head, bone or soft tissue injury. These patients may fall into water, causing submersion injury, or onto hot surface, causing burns. Submersion injury may cause death and is of major concern. In children with epilepsy, the risk of submersion are 7.5 to 13.9 fold higher than in general population (Wirrell 2006). In rural Bangladesh, mortality in adult patients with epilepsy due to accidental injury accounts to 3.8% of all injury deaths. Causes of mortality were drowning and burns. The proportions of death due to drowning in patients with epilepsy was significantly higher than standard population (83% vs 7%) (Mateen et al. 2012).

'Sudden unexpected/unexplained death in epilepsy' (SUDEP) is a sudden unexpected death in epilepsy in which autopsy fails to reveal an anatomic or toxicological cause of death (Timmings 1993, Coyle et al. 1994, Nashef 1997). Recently, Nashef et al. (2012) unified the definition of SUDEP as "Sudden, unexpected, witnessed or unwitnessed,

non-traumatic and non-drowning death, occurring in benign circumstances, in an individual with epilepsy, with or without evidence for a seizure and excluding documented status epilepticus (seizure duration >30 min or seizures without recovery in between), in which post-mortem examination does not reveal a cause of death". 'Benign circumstances' which have been included in the definition refer to instantaneous death in patients with epilepsy without apparent reason. It is the most important epilepsy-related cause of death. This unified definition resolves current ambiguities, helps identify SUDEP cases and prevents misdiagnosis that would lead to SUDEP cases not have been investigated.

SUDEP incidence is common in young patients with refractory epilepsy aged less than 50 years. The overall incidence rate of SUDEP was 2.2 per 1,000 person-years (Derby et al. 1996) in United Kingdom and 0.54 to 1.35 SUDEP per 1,000 person-years in Canada (Tennis et al. 1995). Recently, Tomson et al. (2005) reviewed 14 studies to find the incidence of SUDEP in different epilepsy population. The incidence was 0.35 cases per 1,000 person-years in community-based population, 1–2 per 1,000 person-years in chronic epilepsy, and 3–9 per 1,000 person-years in refractory seizures.

Studies have been carried out to find the risk factors for SUDEP. Tennis et al. (1995) associated male sex, polytherapy and prescriptions of psychotropic substances with SUDEP. Nilsson et al. (2001) put forth factors indicating severe epilepsy as risk factors including high concentration of carbamazepine levels although Opeskin et al. (1999) had not supported it. A recent study by Thomas et al. (2005) had not found association of

SUDEP with any particular antiepileptic drugs. They found the risk factors to SUDEP were seizure frequency, onset at early age and long duration of disorders. Hesdorffer et al. (2012) analysed four case-control studies of SUDEP from USA, Sweden, Scotland and England. They found that the risk factors for SUDEP were increased frequency of generalized tonic–clonic seizures, use of polytherapy, duration of epilepsy, young age at onset, gender, symptomatic etiology, and lamotrigine therapy. Due to its unknown pathological mechanism, methods to prevent SUDEP are directed at its risk factors (Elson et al. 2009).

Suicides have been attributed to epilepsy. Kanner (2010) found that about 12% death in patients with epilepsy was caused by suicide. The risk of committing suicide is 2-fold higher in patients with epilepsy alone compared to general population. This risk increases with the presence of concomitant disease like mood disorder, anxiety and psychotic disorder by 32-fold, 12.5-fold and 11.5-fold, respectively.

In 2008, the U.S. Food and Drug Administration (FDA) issued an alert to health care professionals about an increased risk of suicide ideation and suicide behaviour in patients treated with antiepileptic drugs. Such a conclusion came from a meta-analysis of 11 antiepileptic drugs, namely carbamazepine, felbamate, gabapentin, lamotrigine, levetiracetam, oxcarbazepine, pregabalin, tiagabine, topiramate, valproic acid, and zonisamide for epilepsy, psychiatric indications and ‘‘other conditions’’. In the main analysis, almost 28,000 people taking antiepileptic drugs and 16,000 people taking placebo were considered. There were four completed suicides altogether, all in people

taking antiepileptic drugs and none in those taking placebo. The FDA concluded that patients receiving antiepileptic drugs were twice more likely to experience suicidal behaviour or ideation compared with placebo. In addition, they observed that the relative risk was higher in patients treated for epilepsy compared to psychiatric illnesses or other conditions.

1.1.3 Impact on economic burden and socioeconomic status

Epilepsy increases economic burden to patients and society through direct and indirect cost. Direct cost is incurred in the management of seizure-related events, complications and medical expenses. Indirect cost is incurred due to loss of employment leading to the need for welfare medical fund and low socioeconomic living.

Begley et al. (1999) compared the cost of epilepsy in United States, United Kingdom and Switzerland. In the United States, total lifetime cost of all patients with epilepsy was estimated at $3 billion, in which 62% was the indirect cost. Total hospital cost was estimated at more than $500 million and physician services cost at almost $80 million. The total annual cost for epilepsy in United Kingdom was estimated at $2.9 billion, in which nearly 70% was due to indirect cost. With the average medical cost per patient at $917, a projected total cost of $27 million was estimated for management of seizure disorders in the first year. The total direct cost in Switzerland was $211.1 million, with 46% incurred by patients with intractable seizures. Seventy-two percent of the calculated indirect cost ($113.7 million) was due to unemployment.

Hong et al. (2009) performed cross-sectional cost-of-illness study on 289 patients with epilepsy in China. The calculated annual direct cost was $483 and the indirect cost was $289, making a total of $773 per patient. A similar study in India by Thomas et al. (2001) for 285 patients found that the annual direct cost per patient was $93 and the indirect cost was $251 per patient, lower than those reported in United Kingdom, United States and Germany.

Jennum et al. (2011) calculated the direct and indirect costs associated with epilepsy in Denmark. They found that the net annual healthcare and indirect cost were 15 times higher for patients with epilepsy compared to person without epilepsy. In Nigeria, women with epilepsy have lower socioeconomic status when compared with women with other medical conditions. Women with epilepsy in Nigeria are not employed and had lower mean income. They are socially stigmatized, had fewer years of education, lower marriage rates, physically abused, sexually abuse and had poorer living environment (Komolafe et al. 2012). To my knowledge, there is no data regarding economic burden and socioeconomic status for patients with epilepsy in Malaysia.

1.2 Pharmacotherapy of epilepsy

Numerous guidelines on management of epilepsy in children and adults have been produced by American Academy of Neurology (AAN) and American Epilepsy Society (AES), Scottish Intercollegiate Guidelines Network (SIGN), National Institute for Health and Clinical Excellence (NICE), International League Against Epilepsy (ILAE)

and Consensus Guidelines on the Management of Epilepsy by Epilepsy Council, Malaysia Society of Neurosciences. These guidelines have addressed the proper management and pharmacotherapy in adult and children with epilepsy.

Performing the right diagnosis is the first important step in the epilepsy treatment model (Schmidt 2002). Initiating the right antiepileptic the first time is crucial (Kwan & Brodie 2001). Late treatment leads to suboptimal seizure control and adversely affects the prognosis (Choi et al. 2011). Furthermore, inappropriate prescribing of anti-epileptics incurs significant cost to the healthcare system (Juarez-Garcia et al. 2006).

Prophylactic treatment has been advocated in patients with symptomatic etiology, while immediate treatment (within 1 week of injury) may reduce the risk of post-traumatic seizure disorder (PTSD). Patients should not be treated if the diagnosis is not confirmed. Patients with a certain diagnosis of unprovoked GTCS should be treated after the first seizure if there were previous absence or myoclonic seizures and if recurrence is expected (e.g. in the case of underlying structural brain abnormality). Otherwise, treatment may be initiated after the second seizure. Initiation of treatment for simple and complex partial seizures depends on seizure frequency, severity and patient's preference (SIGN 2003, Epilepsy Council MSoN 2010, NICE 2012). Seizures due to alcohol withdrawal symptoms, seizure induced by metabolic or drug-related cause, and seizure due to sleep deprivation should not be treated with AEDs (Schmidt 2002, SIGN 2003, Epilepsy Council MSoN 2010, NICE 2012).

Patients with recurrent seizures and confirmed diagnosed as having epilepsy should be treated with monotherapy AED, commencing with a low dose and titrated to achieve optimal seizure response and minimal side effects. If the first AED fails to control seizure at maximum tolerated dose, a second alternative AED may be introduced slowly without tapering the first. If the patient has a good response to the second AED, the first AED may be considered to be withdrawn (Schmidt 2002, SIGN 2003, Epilepsy Council MSoN 2010, NICE 2012).

Recent studies have shown the superiority of monotherapy over polytherapy (Brodie et al. 2012), supporting the findings from earlier studies (Covanis et al. 1982, Chadwick 1987, Bourgeois et al. 1987), even though earlier studies have shown otherwise (Deckers et al. 2001). From a total of 1,098 newly diagnosed adolescent and adult patients with epilepsy, 749 (68%) attained at least 1 year seizure freedom, in which 678 (62%) patients were on monotherapy. There was a higher probability of seizure freedom in patients receiving 1 compared to more AEDs ($p<0.001$)(Brodie et al. 2012).

Polytherapy may be initiated in patients with recurrent seizures when treatment with monotherapy regime fails to achieve desired clinical outcome (SIGN 2003, Epilepsy Council MSoN 2010, NICE 2012). Some patients did not achieve seizure freedom (Brodie et al. 2012) while some of them attained fluctuations between seizure freedom and seizure relapse (Sillanpää & Schmidt 2006, Brodie et al. 2012). Seizure control remains suboptimal for many patients with 30 to 40% of them continue to have seizure despite the use of multiple anti-epileptics (Choi et al. 2011). The use of polytherapy may result in poor tolerability of antiepileptic drugs owing to higher incidence of adverse

effects. Strategies to prevent overtreatment (unnecessary and excessive drug load) with antiepileptic drugs should be employed as outlined by Schmidt (2002) because the chance of seizure freedom declined with successive drug regimens, markedly from the first to the third and among patients with localization-related epilepsies (Brodie et al. 2012). Lesser number of previously trialed AED resulted in a better clinical outcome in adult patients with drug-resistant epilepsy (Luciano & Shorvon, 2007). Even though many patients have been treated with two or more AEDs, there is little or no direct evidence that a particular combination is effective in different patients. Stephen et al. (2012) reported 64 successful AED combinations. Approximately seventeen percent patients remain seizure-free on 3 AEDs with 57 separate regimes in the year 2010 compared to 12.7% in year 2000. Levetiracetam (10.2%) and topiramate (7.6%) were the new AEDs commonly represented in successful combinations. Indirect comparisons can be made from RCTs of new AEDs used as add-on therapy in patients with drug-resistant focal seizures (Chadwick et al. 2009). Use of combination therapy should result in optimal seizure outcome (Stephen et al. 2012). The combination of lamotrigine and valproic acid have been shown to be pharmacodynamically synergistic (Pisani et al. 1999, Stephen et al. 2012) and is a rational pharmacotherapy.

Patients with newly diagnosed epilepsy who require treatment can be initiated on standard AEDs such as carbamazepine, phenytoin, valproic acid, phenobarbital, or on the new AEDs lamotrigine, gabapentin, oxcarbazepine, or topiramate. Choice of AED will depend on individual patient characteristics (French et al. 2004a, French et al. 2004b).

1.2.1 Antiepileptic drugs

Both new and old generation AEDs are generally equally effective in managing epilepsy. The newer drugs tend to have fewer side effects (French et al. 2004a, French et al. 2004b). The development of 7 new AEDs (i.e. Gabapentin, Lamotrigine, Topiramate, Tiagabine, Oxcarbazepine, Levetiracetam, and Zonisamide) for epilepsy in 1990s and 2000s (Brodie 2003, French et al. 2004a, French et al. 2004b) has increased by the fact that the prior available old AEDs (i.e. Phenytoin, Carbamazepine, Phenobarbitone, Valproic Acid, Primidone, Ethosuximide) did not provide optimal care for patients with epilepsy. Their seizures were not adequately controlled, or they were experiencing side effects with these older AEDs. In addition to that, the older AEDs have complex pharmacokinetics. Four of the six AEDs available prior to 1990 (phenytoin, carbamazepine, phenobarbital, and primidone) are hepatic enzyme inducers. On the other hand, valproic acid is a potent hepatic inhibitor. Enzyme-inducing and enzyme-inhibiting AEDs produce important interactions with many commonly used medications, such as warfarin, oral contraceptives and calcium channel antagonists. The newer agents are involved in many fewer drug interactions because they have little effect on the CYP450 enzyme system and other metabolic pathways. A few studies (Kwan & Brodie 2000, Kwan & Brodie 2001) have indicated that patients with newly diagnosed epilepsy can be categorized into those who are treatment responsive or treatment resistant. These treatment responsive patients responded to low doses of essentially all the AEDs studied, both old and new. Because these patients will remain on the initial or second therapy for

several years, selecting the most tolerable AED with the least likelihood of negative impact on quality of life is important. The older AEDs have an advantage of broad familiarity, lower cost, known efficacy, wide availability via coverage by third party payers, and long-term experience. French et al. (2004a) reported that the new AEDs may be better tolerated than the standard, with equivalent efficacy. However, they did not compare the importance of other differences between old and new AEDs, such as simpler pharmacokinetics, absence of apparent disturbance of the hormonal milieu, better safety, and the need for less laboratory monitoring. It is difficult to make such comparisons in an evidence-based fashion. The new drugs are all substantially more expensive than the old. There is no literature that addresses the cost-benefit related to these issues. At present, there is insufficient evidence to determine effectiveness in newly diagnosed patients for tiagabine, zonisamide, or levetiracetam (French et al. 2004a, French et al. 2004b). Some AED have been shown to induce exacerbation of seizures (Perucca et al. 1998), such as carbamazepine, phenytoin, vigabatrin, gabapentin and benzodiazepine. This should not be overlooked by the treating physicians.

The choice of AEDs for certain types of seizures and patients have been outlined in numerous guidelines (NICE 2012, SIGN 2003, SIGN 2005, French et al. 2004a, French et al. 2004b, Epilepsy Council MSoN 2010), studies (Chiron et al. 1997, Vigevano et al. 1997, Motte et al. 1997, Nielsen et al. 1997, Beran et al. 1998, Guerrini et al. 1998, Perucca et al. 1998, Frank et al. 1999, Privitera et al. 2003, Poza 2007) and reviews (Brodie & French 2000, O'Brien & Gilmour-White 2005, Cramer et al. 2007, Poza 2007, Stefan 2011).

The AED of choice for generalized seizure is valproic acid and it has been proven superior to topiramate in the Standard And New Antiepileptic Drugs (SANAD) study (Marson et al. 2006). If absence or myoclonic seizures or JME is suspected, lamotrigine, carbamazepine, oxcarbazepine, gabapentin, phenytoin, pregabalin, tiagabine or vigabatrin cannot be initiated because they may exacerbate myoclonic seizures (SIGN 2005, NICE 2012). Nielsen et al. (1997) and Perucca et al. (1998) have also reported that oxcarbazepine, vigabatrin and tiagabine aggravate absence seizures and myoclonic jerks. Absence seizure should be treated with ethosuximide, valproic acid or lamotrigine (SIGN 2003, NICE 2012). Patient with myoclonic seizure should be treated with valproic acid as the first line AED. Levetiracetam and topiramate may be considered as alternative but the latter has less favorable side effect profiles compared to the others (NICE 2012). For infantile spasms, the first line treatment is steroid or vigabatrin for West's syndrome secondary to tuberous sclerosis (SIGN 2005, NICE 2012). Valproic acid has also been suggested as the first line treatment for Dravet syndrome, Lennox-Gastaut syndrome, IGE, JME, childhood absence epilepsy, juvenile absence epilepsy and generalized tonic-clonic (GTC) only (NICE 2012). Felbamate is limited to the management of Lennox-Gastaut syndrome and partial seizures refractory to other AED due to its severe bone marrow and hepatotoxicity effects (French et al. 1999).

The first line treatment for partial seizure is carbamazepine (NICE 2012), but Marson et al. (2007) in the Standard And New Antiepileptic Drugs (SANAD) study has proven that Lamotrigine is superior in tolerability and efficacy compared to valproic acid. On the other hand, Tudur Smith et al. (2007) showed otherwise. Lamotrigine was superior compared to carbamazepine, oxcarbazepine, valproic acid, topiramate, gabapentin,

phenytoin and phenobarbitone in terms of tolerability, but was found inferior compared to carbamazepine in terms of time to achieving a 12-months remission for partial seizures. However, valproic acid, oxcarbazepine and levetiracetam had been suggested as alternative AEDs to carbamazepine in treatment of partial seizures (NICE 2012).

1.2.2 Pharmacotherapy in special populations

The management of women with epilepsy created special problems which are related to their hormonal changes, which start at the menarche and continue until after the menopause. Many women report that their seizure episodes occur in relation to their menstrual periods. The precise reason for catamenial epilepsy is unknown, but may be related to the fact that estrogen is softly epileptogenic, whereas progesterone is weakly antiepileptogenic (O'Brien & Gilmour-White 2005, Cramer et al. 2007). The rapid reduction in serum progesterone concentrations just before a period may make women more susceptible to epilepsy at that time. Changes in fluid balance may also play a part, but giving diuretics starting a week before a period is due is not effective. It may then be reasonable to give an additional AED starting a few days before a period is due. For practical purposes this needs to be a quick acting drug (e.g. clobazam, clonazepam or acetazolamide) that can be given at full dose in addition to the ongoing drug. Menopause tends to occur earlier in women with epilepsy. There is often an unpredictable increase or decrease in seizure frequency at different phase of menstrual cycle and pre-menopause and post-menopausal period (Harden et al. 1999). Valproic acid and polytherapy should be avoided throughout pregnancy to decrease the risk of congenital

malformations and cognitive outcomes (Harden et al. 2009). Phenytoin and phenobarbitone should be avoided during pregnancy to decrease the risk of cognitive outcomes (Harden et al. 2009). AED use is an independent predictor of increased risk of fractures from the effect of AEDs on vitamin D (Persson et al. 2002). AEDs, age and postmenopausal status added to risk of osteoporosis. Therefore, women with epilepsy should have a bone health screen and be advised accordingly (Drezner 2004).

The incidence of epilepsy in elderly has increased steadily over the last few decades. Epilepsy is the third most common neurologic disorder in elderly, after cerebrovascular disorder and dementia. The most common etiology of seizure was stroke. The most common types of seizure were simple partial and complex partial seizure with or without secondary generalization (Stefan 2011). The choice of AED for elderly fundamentally depends on its pharmacokinetic profile and possible side effects (Poza 2007, Brodie et al. 2009, Stefan 2011). AED (e.g. valproic acid) which causes metabolic side effects may lead to acquiring diabetes, cardiovascular mortality and osteoarticular problems in elderly patients (where the risk is already high) is not recommended. AED with cognitive side effects (e.g. Phenobarbitone, Topiramate, Tiagabine) and osteoporosis (e.g. Phenobarbitone) are not suitable for elderly patients. AED which enable rapid dose titration and allow intravenous administration, such as phenytoin, may have some value but limited due to its complex pharmacokinetic profile. Carbamazepine has minimal cognitive effect but it has hepatic capacity causing high interaction with other drugs. Lamotrigine does not cause cognitive side effects but its hepatic metabolism may be of concern (Anderson et al. 2002). Newer AED with favorable linear kinetics and lower potential for side effects (e.g. lamotrigine, levetiracetam, pregabalin, oxcarbazepine) is

highly suitable for this population (Poza 2007). On the other hand, Stefan (2011) recommended low dose valproic acid (30 to 40% less than usual adult dose) as the most effective AED for elderly compared to phenytoin. Newer AED of choice are lamotrigine and gabapentin (Brodie et al. 2009, Stefan 2011). Based on US rating between 2000 and 2004, the first line AED used for elderly patient were lamotrigine, levetiracetam, gabapentin, carbamazepine and oxcarbazepine, followed by topiramate and valproic acid. In German, Austria and Swiss, the rating in 2007 showed the first line AED used for elderly were levetiracetam, lamotrigine and gabapentin, followed by topiramate and valproic acid. Oxcarbazepine and carbamazepine were not recommended due to hyponatremia, cardiac disorders and drug interactions (Stefan 2011).

The prognosis of seizure freedom in patients with newly diagnosed epilepsy varies widely from 22% to 80% (Elwes et al. 1984, Mattson 1994). Early control may affect long term prognosis. The longer the seizures continue after the start of treatment, the less likely it is controllable (Elwes et al. 1984, Luciano & Shorvon 2007, Choi et al. 2011). Del Felice et al. (2010) reported that the cumulative probability of 2-year remission in newly diagnosed patients with epilepsy was 56.3% at 2 years after start of treatment, and 62.6, 69.4 and 79.5% at 3,5 and 10 years, illustrating a slow progression in overall achievement as duration of disease prolonged. Luciano & Shorvon (2007) found that shorter duration of epilepsy was associated with a better clinical outcome in adult patients with drug-resistant epilepsy.

Seizures which continue beyond 2 to 3 years are considered as chronic epilepsy. Appropriate review of clinical aspects of the illness and pharmacotherapy must be worked out (Epilepsy Council MSoN 2010). Adequate drug trials should be advocated (SIGN 2003, Epilepsy Council MSoN 2010, NICE 2012). Del Felice et al. (2010) reported that the cumulative probability of 2-year remission in newly diagnosed patients with epilepsy was 56.3% at 2 years after start of treatment, and increased at a slower rate up to 10 years to 79.5% with adequate pharmacotherapy.

When seizure freedom has been sustained for a period of at least 2 years, drug withdrawal may be considered (Epilepsy Council MSoN 2010). When AED is being discontinued, it should be tapered down slowly (at least 2 to 3 months) and done so with one drug at a time (SIGN 2003, NICE 2012).

1.2.3 Antiepileptic drugs utilization pattern

The pattern of AED use differs between countries (Malerba et al. 2010, Ayadurai et al. 2011, Landmark et al. 2011) and between neurologists (Smeets et al. 1999). In Norway, Landmark et al. (2011) evaluated more than 4 million prescriptions of antiepileptic drugs from 2004 to 2009. They found that the four most commonly used antiepileptics drugs were carbamazepine, valproic acid, lamotrigine and levetiracetam which contributed to 68% of total antiepileptics used. The most common combination therapies were lamotrigine and valproic acid (42%), and carbamazepine and levetiracetam (19%). Newer antiepileptics were more commonly used in women compared to men. In children, most commonly used antiepileptics were valproic acid and lamotrigine.

Malerba et al. (2010) did a similar evaluation on the pattern of antiepileptic drug prescriptions for 933 adult and 191 children with refractory epilepsy in 11 tertiary centers in Italy. Their findings were similar to the other author. Most commonly used antiepileptics were carbamazepine, valproate, lamotrigine and levetiracetam. The used of antiepileptic drugs in adult were levetiracetam (35%), carbamazepine (34%) and lamotrigine (30%). In children, valproic acid (46%), carbamazepine (27%), topiramate (21%) and phenobarbitone (20%) were used. For treatment of partial epilepsy, carbamazepine (37%), levetiracetam (33%) and lamotrigine (26%) were used. In generalized epilepsy, valproic acid (62%), lamotrigine (33%) and levetiracetam (28%) were used. Polytherapy was used in 79% adult and 73% children. Second generation antiepileptic drugs were used in 81% adult and 54% children.

In Malaysia, antiepileptic drug utilization has been described by Ayadurai et al. (2011) and Ab Rahman et al. (2005). Ayadurai et al. (2011) described AED utilization in 618 patients aged between 12 and 85 years old, seen in Penang Hospital. Most commonly used antiepileptic drugs were carbamazepine (28%), valproic acid (39%), phenytoin (24%) and lamotrigine (9%). More than 55% patients were on monotherapy and 41.1% on polytherapy. Ab Rahman et al. (2005) described AED utilization in 180 children and young adolescent aged between 6 months to 19 years. 64% of them were on monotherapy in which valproic acid were commonly prescribed (36%), followed by carbamazepine (21%), and other less frequently prescribed AED such as clonazepam and phenobarbitone. Majority of 22% patients on dual therapy were on combination of valproic acid with another AED such as clonazepam and carbamazepine.

1.3 The role of valproic acid in the treatment of epilepsy

Despite its use for almost 50 years, valproic acid remains an important drug in the treatment of epilepsy. It was previously known as n-dipropylacetic acid (DPA). Its anticonvulsant effect was first discovered in 1963 (Loiseau et al. 1975, Rogvi-Hansen & Gram 1995, Brodie 2010) and was used as early as 1967 in France (Löscher 2002, Perucca 2002, Brodie 2010), 1974 in Norway (Henriksen & Johannesen 1982), 1977 in UK and 1978 in USA. In Malaysia, valproic acid was registered and marketed in 1986 (National Pharmaceutical Control Bureau, 2013).

1.3.1 Pharmacology of valproic acid

Valproic acid works via a combination of several neurochemical and neurophysiological mechanisms. It acts on diverse regional targets involved in the induction and propagation of seizures (Löscher 2002). This may explain its broad spectrum efficacy for several types of seizures because of its ability in counteracting diverse molecular and cellular pathophysiology that happens during seizure event.

Valproic acid acts in balancing inhibition and excitation of neurons in the brain regions involved during pathogenesis of seizure by; (i) increasing turnover of γ-aminobutyric acid (GABA) and potentiates its function to control seizure generation and propagation in some specific brain regions, (ii) controlling neuronal excitation mediated by N-

methyl-D-aspartate (NMDA) subtype glutamate receptor, (iii) reducing the release of γ-hydroxybutyrate (GHB) which has been suggested to be involve in the modulation of absences seizures, and (iv) blocking voltage-dependent sodium currents (Löscher 2002, Perucca 2002, Johannessen & Johannessen 2003). Valproic acid is rapidly metabolized into pharmacologically active metabolite found in various body tissues namely (E)-Δ^2-VPA, Δ^4-VPA and other metabolites such as 3-hydroxy-VPA, 4-hydroxy-VPA 5-hydroxy-VPA 3-oxo-VPA, 3-keto-VPA, and others (Löscher 1981, Nau & Löscher 1984, Baillie & Rettenmeier 1989, Semmes & Shen 1991). Both valproic acid and its metabolite limit the firing of neurons which trigger seizures in a concentration-, voltage-, rate- and time-dependent fashion (Löscher 2002).

Trans-2-en-valproate, i.e. (E)-Δ^2-VPA, is the most potent valproic acid metabolite and has got higher potency than the parent drug (Baillie & Rettenmeier 1989, Löscher 2002). Since (E)-Δ^2-VPA is cleared from the brain and plasma more slowly than the parent drug, it has been proposed that this metabolite accumulates with time in CNS and contributes to therapeutic effects of the parent drug. The relatively slow washout kinetics of (E)-Δ^2-VPA as compared to the parent drug may account for the persistence of anticonvulsant activity following discontinuation of valproic acid administration (Baillie & Rettenmeier 1989). It is found in appreciable quantities in human brain (Baillie & Rettenmeier 1989) but considered not significant for the effects of valproic acid (Löscher 2002). Nevertheless, the presence of metabolite might explain the poor correlation between anticonvulsant activity with valproic acid serum concentration and the lengthy time course for anticonvulsant effect which differs from valproic acid pharmacokinetic, i.e. protection against seizure is not maximal until some times after the

attainment of steady-state concentration in serum or brain tissues, and persist long after the parent drug has been cleared from the systemic circulation (Nau & Löscher 1984, Pollack et al. 1986).

Valproic acid exhibit 'early' (i.e. occurring immediately after first administration of effective dose) and 'late' (i.e. developing during long-term administration) anticonvulsant effects. Löscher & Hönack (1995) reported marked increase in valproic acid anticonvulsant activity on the second day of treatment and days after, regardless of plasma concentration. Such increase in anticonvulsant activity was also observed by Davis et al. (1994) and Bourgeois et al. (1987). This means that a valproic acid dose or serum concentration being ineffective after a single-dose administration can become effective on long-term administration. This phenomenon may be explained by the time taken by valproic acid to reach its extracellular (e.g. ion channels) and intracellular (e.g. GABA synthesis) sites of action (Löscher 2002, Perucca 2002). Valproic acid uptake into the brain is facilitated by medium- and long-chain fatty acid selective anion exchanger via active transport system at the brain capillary epithelium. This explains how valproic acid enters the brain and reaches its extracellular sites so quickly (Lindberger et al. 2001, Löscher 2002, Perucca 2002) leading to the 'early' anticonvulsant effect after a single dose. The 'late' anticonvulsant effects most likely arise from its slow penetration into the neurons' intracellular sites of action (Löscher 2002, Perucca 2002) and the effect of metabolites (Nau & Löscher 1984, Pollack et al., 1986).

1.3.2 Efficacy of valproic acid

Numerous clinical trials have suggested that valproic acid has antiepileptic activity in both children and adult with epilepsy (Covanis et al. 1986, Henriksen & Johannessen 1982, Bourgeouis et al 1987, Marson et al. 2006, Marson et al. 2007, Levisohn & Holland 2007, Ollivier et al. 2009). Valproic acid has a broad spectrum of antiepileptic effects. It is effective against generalized and partial seizures, refractory syndromes like Lennox-Gastaut syndrome and West syndrome and mixed seizure types which have highly refractory symptoms (Covanis et al. 1986, Bourgeouis et al. 1987, Chadwick 1987b, Löscher 2002, Perucca 2002, Nicolson et al. 2004, Ma et al. 2010). Furthermore, there is no contraindication to the use of valproic acid in any types of seizures or epilepsy (Perucca et al. 1998, Brodie & French 2000). Most adult requires 15 to 30 mg/kg/day in 2 to 3 divided doses (Covanis et al. 1982, Bourgeouis et al. 1987, Eadie 1998), to a maximum of 60 mg/kg/day. It is usually initiated with 400 to 600mg/day, to a maximum maintenance dose of 2500mg/day in divided doses (Epilepsy Council MSoN 2010).

Many studies support the use of valproic acid monotherapy for the treatment of epilepsy. Covanis et al. (1982) assessed 336 patients who received valproic acid. From 71% patients with valproic acid monotherapy, 83% achieved complete seizure freedom. The seizure freedom was achieved in 47% patients with partial epilepsy, more than 80% patients with generalized epilepsy and 72% patients with photosensitivity epilepsy. Similar findings were reported by Bourgeois et al. (1987), where 83% patients with

epilepsy achieved seizure freedom with valproic acid monotherapy. This included 56% patients who were switched from other antiepileptic drugs due to inadequate seizure control and intolerable side effects.

An open clinical trial on 100 children who were on long term monotherapy and polytherapy valproic acid (Henriksen & Johannessen 1982) found that 71% had more than 50% seizure reduction, which included 33% who had total seizure freedom. 36% patients on monotherapy achieved good seizure control. 92% patients with absence seizure had better outcome compared to grand mal (67%), simple partial seizure (54%) and complex partial seizure (74%). Chadwick (1987b) had reviewed 4 open studies of valproic acid monotherapy which cover 527 patients for a minimum follow-up duration of 2 years. More than 80% of patients with primary generalized seizures achieved seizure freedom while patients with partial seizures achieved a lesser extend of 75%.

Marson et al. (2006) provided a data on valproic acid through a multicenter study of early epilepsy and single seizures (MESS). The result significantly showed that patient treated with valproic acid immediately after diagnosis was associated with achieving 1-year and 2-year remission sooner compared to delayed treatments. Valproic acid had been successful in treating photoconvulsive response in photosensitive patients at a higher rate in valproic acid naïve patients (78%) compared to 28% in previously valproic acid exposed patients (Rowan et al. 1979).