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Pattern of anti-epileptic drug usage in a tertiary referral hospital in Singapore

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Abstract

This study describes the anti-epileptic drug (AED) usage pattern of an individual neurologist in a tertiary referral hospital in Singapore. Two hundred and thirty six epilepsy patients seen as outpatients between June and November 1995 and who were taking AEDs were included. One hundred and forty eight patients (62.7%) were on monotherapy, 60 (25.4%) were on two drugs and 28 (11.9%) were on three or more drugs. Carbamazepine (52%), Valproate (24.3%) and Phenytoin (22.3%) were most frequently used as monotherapy. Carbamazepine was most frequently prescribed for patients with partial seizures and Valproate for generalized seizures without partial onset. The commonest 2-drug combination was Carbamazepine and Valproate. Benzodiazepines were used as adjuvant therapy. Forty three patients (18.2%) were taking, and another 22 (9.3%) had tried newer AEDs such as Gabapentin, Lamotrigine or Vigabatrin as add-on therapy.

*Keywords:*Anti-epileptic Drug, Usage Pattern, Epilepsy, Singapore

INTRODUCTION

Amongst various factors affecting anti-epileptic drug (AED) usage, the availability and affordability of AEDs as well as place of practice and preference of treating physicians are most important. This study describes an AED usage pattern of an individual neurologist in a tertiary referral hospital in Singapore and compares this with other AED usage patterns in previous published studies.

MATERIALS AND METHODS

Epilepsy patients seen by one of the authors (SHL) at the Department of Neurology, Singapore General Hospital and were taking AEDs during the period between June and December 1995 were included. Patient's biological data and their epilepsy information were recorded. A diagnosis of focal epilepsy was made based on the presence of (i) a definite history of having partial seizures (with or without secondarily generalization), (ii) focal inter-ictal epileptiform discharges (IED) on routine EEG or (iii) both. A diagnosis of generalized epilepsy was made when the patients had generalized seizures (myoclonic, absence, or generalized tonic-clonic without partial onset) and/or presence of only generalized IEDs (such as generalized 3 Hz spike & wave complexes or poly-spikes).

With regards to treatment, the author adopted a common approach in AED prescription. AEDs were chosen based mainly on their efficacy for the seizure type(s) and their side effect profile. Whichever AED was chosen, it was given initially as monotherapy. Dose of each AED was increased till seizures were controlled or unacceptable side effects appeared, regardless of the AED blood level. If an AED was available in control-release (CR) formulation, it would be used when patients could afford. When one AED failed to give satisfactory control of seizures at maximum tolerated dose, an alternative monotherapy was tried. Combination therapy was used when 2 or 3 different monotherapies failed to control seizures. Drugs chosen for combination therapy were based on their presumed complimentary mechanisms of action as well as minimal drug to drug interaction.[1]

In this study Phenytoin (PHT), Phenobarbitone (PHE), Carbamazepine (CBZ), Valproate (VPA), and Primidone (PRI) which have been used in Singapore for more than 10 years were considered as "Conventional" or "Older" AEDs. Gabapentin (GBP), Lamotrigine (LTG) and Vigabatrin (VGB) which became available in the last 3-4 years were classified as "Newer" AEDs. Clobazam (CLB) and Clonazepam (CLN) were grouped as Benzodiazepine group of drugs (Table 1). The number and types of AED used, and their highest

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dosage during the study period were described.

RESULTS

Two hundred and thirty six patients, 128 male and 128 female, with a median age of 28 years (range 6-76 years) were studied. The racial distribution of these patients was as follow: Chinese 202, Indian 16, Malay 10 and others 8. The median age of onset of epilepsy was 14 years (range : 1-72 years) and the median duration of epilepsy was 11 years (range : 1-44 years). One hundred and eighty eight (80%) patients had focal epilepsy while the rest (20%) had generalized epilepsy.

One hundred and forty eight patients (62.7%) were on monotherapy, 60 (25.4%) were taking 2 AEDs and 28 (11.9%) were prescribed 3 or more AEDs. Carbamazepine was the commonest monotherapy (52%) followed by Valproate (24%) and phenytoin (22%) (Table 1). Carbamazepine was primarily prescribed for partial seizures whereas Valproate was for generalized seizures. The median and the range of each monotherapy dosages are also shown in Table 2. Carbamazepine with Valproate was the most frequent 2-drug combination (Table 3) while Carbamazepine, Valproate with one of the newer AEDs were the commonest 3-drug combination. Other types of combination are shown in Table 3 & 4. Forty three patients (18.2%) were taking newer AEDs (GBP, LTG, VGB) as add-on therapy. Another 22 patients (9.3%) had tried newer AED in the past, also as add-on therapy.

DISCUSSION

The main aim of treatment of epilepsy is to make the patient completely seizure-free, or to reduce seizure frequency and severity if the patient's seizures can not be completely suppressed. The standard treatment of epilepsy is optimal use of AED(s). Choice of drugs usually depends on drug (such as availability & accessibility, efficacy, side effect profile and ease of use) as well as patient factors (Table 5).

Availability and accessibility of an AED is mainly determined by the success of drug registration process in that country, the presence and location of the relevant pharmaceutical company within the country, and inclusion of the drugs by hospital/clinic into its standard formulary. Efficacy refers to the effectiveness of an AED in preventing or reducing the recurrence of a particular seizure type. For example, VPA are usually chosen for generalized seizures and CBZ or PHT for partial seizures. Potential AED side effects and their appearance not only affect the physicians' choice but also determine the acceptance of the drug by the patient. For example, potential teratogenicity may make physicians avoid using VPA in female patients who are planning to have children. However not all patients will develop side effects and not all side effects are unacceptable. For example weight gain and hirsutism are probably less acceptable in female patients than in the males. Preparation of AEDs also affect the severity of dose related side effect. Physicians may choose an AED with control-release formulation as the occurrence of dose related side effect are less likely and higher dosages of that AED are possible. Ease of use of an AED affect the patient's compliance to medication. For example, physicians usually prefer to use AEDs that have long half-life thus medication can be given once per day to improve compliance.

Other factors affecting AED usage include preference and place of practice of the prescribing physicians. The former can be influenced by where and how the physicians (neurologists and non-neurologists) received their training in neurology and epilepsy while the latter determines the AED needs of patients. For example in Singapore, patients seen at primary care services and managed by general practitioners or doctors at government polyclinics usually have less severe epilepsy. Patients are often prescribed conventional or older AEDs. Dosage of these AEDs are generally not high

TABLE 1: Types of AEDs used in this study

"Conventional" or "Older" AEDs	"Newer" AEDs	Benzodiazepine
Carbamazepine (CBZ) Phenytoin (PHT) Phenobarbitone (PHE) Valproate (VPA) Primidone (PRI)	Gabapentin (GBP) Lamotrigine (LTG) Vigabatrin (VGB)	Clobazam (CLB) Clonazepam (CLN)

TABLE 2: Monotherapy

Drug	Patient No.			%	Dosage (mg/day)	
	Partial Sz	Gen. Sz	Total		Median	Range
CBZ (CR)	61	1	62	41.9	800	200-1800
CBZ	15	–	15	10.1	800	400-1200
VPA	10	14	24	16.2	800	400-3000
VPA (CR)	3	9	12	8.1	500	500-2000
PHT	24	9	33	22.3	300	100-530
PRI	2	–	2	1.4	500	500-750
Total			148			

Note: For abbreviations, please see text.

TABLE 3: Two-drug Combination

Drugs	Patient No. (%)
2 Conventional AEDs	
• CBZ or CBZ (CR) + VPA	25 (41.7)
• Others	6 (6.0)
1 Conventional AED + 1 Newer AED	19 (31.6)
1 Conventional AED + 1 Benzodiazepine	10 (16.7)
Total	60 (100)

Note:

Conventional AEDs : CBZ, PHT, VPA, PHE, PRI
Newer AEDs : GBP, LTG, VGB
Benzodiazepine Group of Drugs : CLB, CLN
For abbreviation, please see text

TABLE 4: Three or Four Drug Combination

Drugs	Patient No. (%)
2 Conventional AEDs + 1 Newer AED	16 (57.1)
1 Conventional AED + 1 Newer AED + 1 Benzodiazepine	5 (17.8)
2 Conventional AEDs + 1 Benzodiazepine	4 (14.3)
1 Conventional AED + 2 Newer AEDs	1 (3.6)
4 AEDs	2 (7.2)
Total	28 (100)

Note:

Conventional AEDs : CBZ, PHT, VPA, PHE, PRI
Newer AEDs : GBP, LTG, VGB
Benzodiazepine Group of Drugs : CLB, CLN
For abbreviation, please see text

TABLE 5: Factors affecting AED usage

- Drug factors
  - Availability and accessibility within a country, state, city, hospital, clinic, etc.
  - Efficacy
  - Potential side effects
  - Ease of use
  - Formulation of AED
- Patient factors
  - Types and severity of seizures and epilepsy
  - Age
  - Sex
  - Compliance
  - Acceptability of AED side effects
  - Pregnancy
  - Concurrent systemic illness
- Preference, training and experience of treating physician
- Availability of other treatment options
- Economic factors
  - Cost of AED
  - Affordability of patients

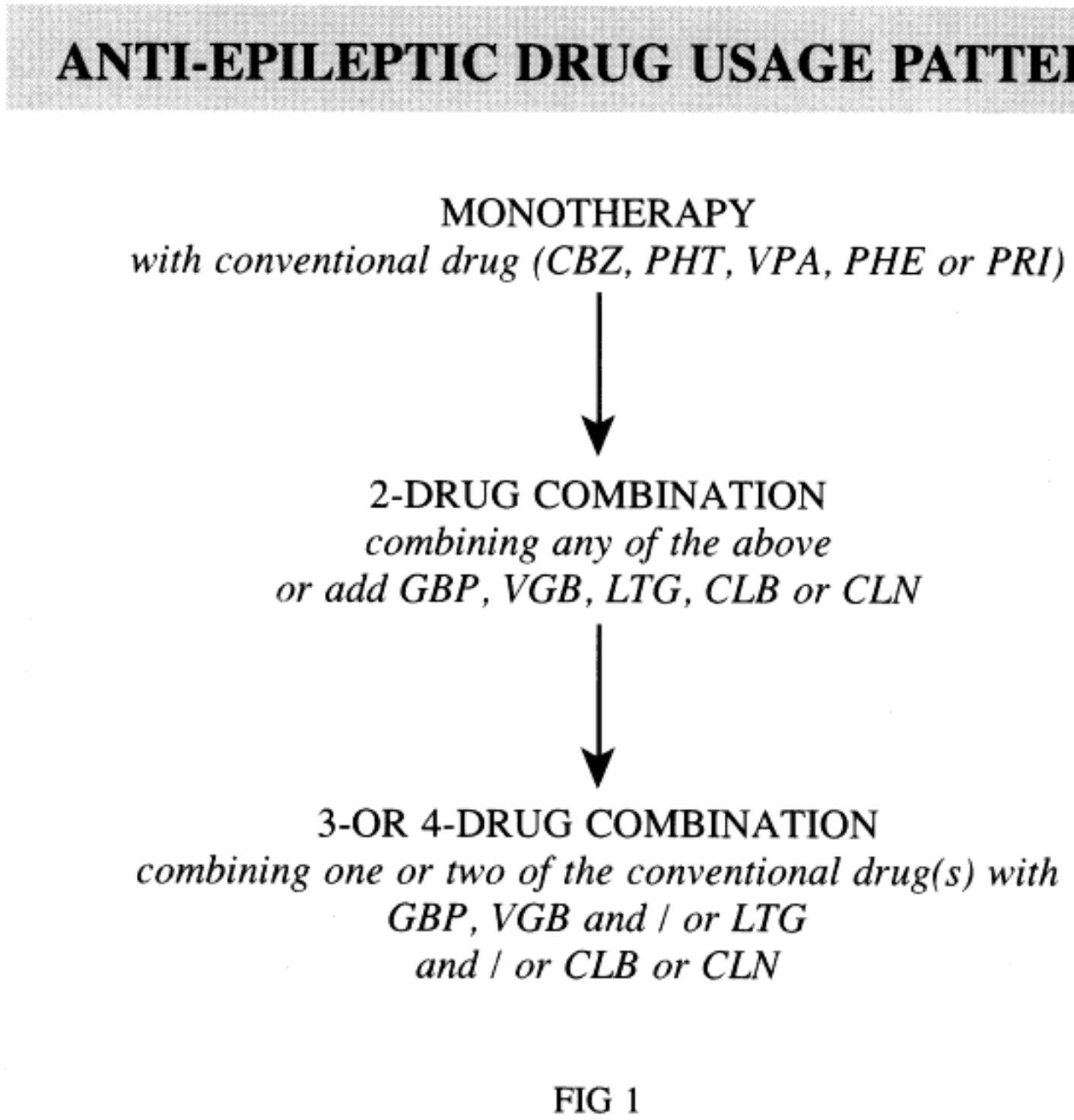

FIG 1

TABLE 6: Comparison of different drug usage pattern

Authors, Reference	Types, Year & Place of Study	Prescribing Physicians or Prescription No.	Patient No.	Mono-Rx	Poly-Rx	3 commonest AEDs used (** mono-Rx)
Hart & Shorvon[4]	Patient & GP survey, UK	119 GPs	1600	65%	35%	CBZ PHT VPA
Chadwick[5]	GP survey, 1993 UK	254 GPs	#	72%	27%	**PHT (38%) **CBZ (34%) **VPA (21%)
MRCAEDWS[6]	AED Withdrawal Study, 1984-1988, UK	125 clinicians	1013	83%	17%	**CBZ (31%) **PHT (31%) **VPA (24%)
USANPA[7]	National Prescription Audit, 1992, USA	19,100,000 Prescriptions	#	#	#	**PHT (48.4%) **CBZ (32.5%) **VPA (13.3%)
Imam Sjahrir[9]	Doctor's Survey, 1995 A city in Indonesia	22 Neurologists 21 GPs 13 Paediatricians	#	#	#	PHT CBZ CLB
San Luis[10]	Hospital-based & Prescription data, 1992-1995, Philippines	GPs (61%) Paediatricians (17%), Neurologists (17%) Internists (5%)	#	#	#	PHE (48%) PHT (25%) CBZ (20%)
Menon, Saw & Tan[11]	Community-based 1995, A state in Malaysia	GPs Internists	1049	#	#	PHT (29%) CBZ (24%) PHE (24%) VPA (23%)
Visudhiphan & Chiemchanya[12]	Hospital-based, 1981-1982, Thailand	Paediatricians	141	#	#	**PHE (78%) PHT (11%) VPA (9%)
Puvanendran[8]	Hospital-based, EEG Lab data, 1989-1991, Singapore	Internists Paediatricians Neurologists	565	88%	12%	**PHT (43%) **PHE (38%) **CBZ (12%)
Lim, Tan & Chen (this study)	Hospital-based, 1995, Singapore	1 Neurologist	236	63%	37%	**CBZ (52%) **PHT (24%) **VPA (24%)

Note:

MRCAEDWS: Medical Research Council Anti-epileptic Drug Withdrawal Study
USANPA: USA National Prescription Audit
G.P.: General Practitioners
#: Data not available

and newer AEDs are rarely used. Patients whose seizures that are not well controlled are more likely to be referred to tertiary referral hospitals where they are managed by neurologists (adult or pediatric). These patients are more likely to receive 2 or more AEDs or higher dosages. Tertiary referral hospitals are also places where neurologists have easier assess to newer AEDs or are asked by pharmaceutical companies to conduct drug trials (usually open-labeled). These will indirectly influence their prescribing habit.

In addition, the availability of other treatment options such as epilepsy surgery might affect the AED usage pattern. The commonest type of epilepsy surgery is temporal lobectomy. It has been reported that patients with mesial temporal lobe epilepsy have excellent result from temporal lobectomy.[2] If pre-surgical evaluation facilities and surgical expertise are available, potentially good surgical candidates are likely to be offered surgery as an alternative to long-term usage of newer AEDs.

One of the most important factors in deciding which drug to prescribe is cost of AEDs and affordability of patients. Although newer AEDs might be more efficacious and less toxic than older AEDs, their usage in this part of the world is limited by their relatively high cost. In Singapore, older AEDs such as PHT, PHE, CBZ, and VPA are subsidized by government whereas newer AEDs are not. Tan et al has estimated the cost of drug treatment using the AED usage pattern described in this study (3). For monotherapy without using newer AED, the estimated average cost per patient would be $270/year (range : S$130-S$450). For a 2-drug combination without newer AED, S$570/year (range : S$180-S$780), and with newer AED, S$2000/year (range : S$500-S$2800). Thus the cost of having one newer AED in a 2 drug-combination is 4 times the cost of 2-drug combination without a newer AED. As this was a retrospective study, we did not have data on the patient's family income. However patients who required 2 or more AEDs were likely to be unemployed or under-employed, and dependent on other family members' financial support. Thus taking newer AED on a long term basis can be quite costly for many patients and their families.

It is probably easier to describe an AED usage pattern of a doctor than to compare AED usage patterns of different studies from different institutions and countries. This is because the aim, design, material, source of information, method, place and years of studies are different. Table 6 summaries the relevant information on AED usage patterns described in United Kingdom[4-6], United States[7] and this part of the world[8-12] to illustrate that AED usage patterns are always different and unique. Even in the same country or institution, AED usage pattern might not be the same amongst different physicians and will also change over time. Despite the differences in AED usage, it is still important to know the prescribing pattern so as to estimate the cost of medical treatment of epilepsy in that country or community.

It is important to maintain patients on monotherapy as compliance is better, side effects are less and there is no problem of drug-to-drug interaction. In United Kingdom and Singapore, monotherapy was commonly used by non-neurologists (Table 6). One would expect that patients seen by neurologists in a tertiary referral setting are more likely to have difficult to control seizures requiring polytherapy. However, in this study, majority of the patients were on monotherapy (63%). It is the authors' experience that many of the patients referred for management of "failed" monotherapy had not been given maximum tolerated dose of AED. Regardless of the blood level, by increasing the dosage of the same AED gradually to maximum tolerated dose, seizures could be controlled in many patients. We wish to emphasize that there is no standard dose for any AED. Every patient has his/her own necessary dose. For example, the dose of PHT ranged from 100 mg to 530 mg even though most patients needed 300 mg per day (Table 2). Some patients could not tolerate more than 200 mg of PHT per day while others could take more than 400 mg per day with no unacceptable side effects.

Use of control-release (CR) formulation also improved seizure control in many patients. For example, a patient was given CBZ 400 mg three time a day (total 1200 mg per day) but continued to have seizures. He could not tolerate beyond 400 mg at each dose. However after conversion to CR formulation, he could tolerate 800 mg given twice daily (total 1600 mg per day) and had no seizures. For this reason, majority (80%) of patients on CBZ received the CR formulation (Table 2). The limiting factor in using control-release formulation is the cost which is usually higher than non-CR formulation. When a patient does not require high dosage of AED to control seizures, a CR formulation is preferable (if affordable) as less frequent doses will be needed and compliance will be better.

Another reason for the high percentage of

monotherapy in this study is that the author could convert several patients with polytherapy to monotherapy. When patients on 2 or more AEDs being referred for further evaluation because of poor seizure control, the author would first decide whether these patients' seizures could actually be controlled with monotherapy. For example, when 1 or 2 of the AEDs in the combination regime was/were prescribed at a dose or level that were not "high" for that patient, these AEDs would be stopped after cautious dose reduction. At the same time the dosage of the remaining AED would be increased to the maximum tolerated dose. Alternatively, if an AED was added only recently and had not reached the maximum tolerated dose while the other AEDs had been tried adequately, the most recently added AED dosage would be increased while other AEDs would be gradually stopped.

Our data shows that CBZ was the commonest AED used in monotherapy (52%) or in combination therapy, followed by VPA and PHT. In contrast, the 3 commonest AEDs prescribed in late 1980s and early 1990s in Singapore were PHT (43%), PHE (38.4%) and CBZ (24%).[8] Although the usage pattern in this study is a neurologist's prescribing habit, several other neurologists have indicated that they would also use CBZ as first-line AEDs for partial seizures and VPA for generalized seizures in Singapore (personal communication). The author adopted this usage pattern several years ago based on the results of the two VA studies. The first of these compared CBZ, PHT, PHE and PRI in patients with partial and generalized tonic-clonic seizures.[13] It was found that patients taking CBZ or PHT had less side effects than those taking PHE and PRI. The other finding was that CBZ was significantly more likely than the other three AEDs to render patients free of partial seizures. The second VA study compared CBZ with VPA in patients with partial epilepsy.[14] Although there was no significant difference in the reduction of tonic-clonic seizures between the two drugs, the result for complex partial seizures showed a significant reduction in the frequency of seizures in favor of CBZ. As 80% of the patients in this study had partial seizures (with or without secondarily generalization), it explained the high usage of CBZ.

Despite the two VA studies, it is our experience that other conventional AEDs such as PHT, VPA and Barbiturates are not less effective than CBZ in controlling of partial seizures. Several subsequent studies had failed to demonstrate superiority of CBZ over VPA in controlling partial seizures.[15-17] Where differences in efficacy might be marginal, the importance of comparative toxicity, cost and ease of use of these drugs for a particular patient becomes a major consideration. It needs to be emphasized that when one monotherapy does not control seizures or when unacceptable side effects appear, another monotherapy should be tried before attempting combination therapy. It is our experience as well as others that patients who failed one conventional AED because of inadequate efficacy or unacceptable side effects responded well to another conventional AED.[18]

New AEDs like GBP, LTG and VGB were used or had been tried in more than a quarter of our patients. The efficacy and safety of these newer AEDs have been discussed in a number of reports.[19-27] It is not our intention to review individual drug except to mention some practical points in their usage. As mentioned, the main limiting factor for their usage is cost. Thus they were used as an add-on treatment for patients with partial seizures with or without secondarily generalization not responding to conventional AEDs. GBP had slight advantage over LTG in having no interaction with conventional AEDs in a combination regime. However some patients needed higher dose (>2400 mg/day) to demonstrate a beneficial effect (which many of them could not afford). LTG, on the other hand, had the advantage of able to be used to treat all seizure types. Allergy to LTG, especially in the presence of VPA, was encountered in a few patients. VGB which have been reported to be slightly more efficacious than LTG and GBP in controlling partial seizures, caused unacceptable psychiatric side effects such as irritability. It is the authors' experience that differences in efficacy of these three drugs are marginal. A number of patients had to try these newer AEDs at different time to find out which one actually worked best for them with acceptable side effects. Ultimately it is still the cost of AEDs that determine whether a patient could be maintained on long-term newer AED(s).

Benzodiazepine such as CLB and CLN were used as add-on therapy in a minority of patients (19 patients or 8%) in this study. However, it is not uncommon for some Asian neurologists/ medical practitioners (e.g. in Vietnam, Indonesia, China) to use oral diazepam for long term prophylactic treatment of partial and generalized epilepsy, and use CLB for petit mal epilepsy.[9] Because of their sedative side effects and the tendency of patients to develop tolerance to their effects over a relatively short period of

time, chronic usage might not be advisable. They (CLN, CLB, Diazepam and Nitrazepam) can be used as adjuvant treatment for generalized seizures (typical & atypical absence, myoclonic, tonic, atonic and tonic-clonic seizures) for a "short" period of time. In addition, CLB has been shown to be effective in partial seizures not responding to other AED treatment.[28-30] Thus it is worth including CLB in the list of AEDs to be tried when deciding on medical intractability for the purpose of epilepsy surgery.

In summary, our study shows that even in a tertiary referral hospital, monotherapy is achievable in the majority of patients. Despite the recent availability of newer AEDs in Singapore, older AEDs like CBZ, PHT and VPA are still the commonest AEDs prescribed in a tertiary referral setting. Perhaps it is the optimal integration of older and newer AEDs that is more beneficial than using older or newer AEDs alone. Despite the relatively high cost, it is always good to have more newer AEDs as their presence allows physicians to have wider choices for patients not responding to other AEDs. We are hopeful that cost of AEDs would become a less important issue in AED selection in the very near future. Figure 1 summaries the approach to AED usage in this study.

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