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Is a Fourth-line Antiepileptic Drug Regimen Truly Ineffective for All Types of Epilepsy? Reappraisal of Pharmacoresistance as Related to Epilepsy Type in Adult Patients

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Objective: To examine whether change in antiepileptic drug (AED) up to the fourth regimen effectively increases the opportunity for seizure freedom based on seizure type.

Methods: After excluding those with age-dependent focal epilepsy (e.g., BECT) and epileptic encephalopathy (e.g., Lennox syndrome), we examined the case records of 468 patients and classified them into the temporal lobe epilepsy (TLE) group ($n=153$), juvenile myoclonic epilepsy (JME) group ($n=33$), and those without either TLE or JME (non-J-non-T group) ($n=263$). Any change of AED after initiation of pharmacotherapy, either substituted or added, was counted as one change and regarded as one regimen, while dose change of the same AED was not counted.

Results: In the TLE group, there were significant differences for seizure-free ratio between the first and second regimen ($p<0.001$), second and third regimen ($p<0.001$), and third and fourth regimen ($p<0.001$). There were also significant differences for seizure-free outcome in the non-J-non-T group between the first and second regimen ($p<0.001$), and second and third regimen ($p<0.001$), but not the third and fourth regimen. In contrast, no significant difference was found between the regimens for longitudinal change of seizure-free ratio in the JME group.

Discussion: We found that even administration of a fourth regimen significantly increased the seizure-free ratio in the TLE group, whereas the initial AED regimen was most likely to be successful in patients with JME. Although whether this striking trend of late remission in the TLE group was intrinsic in nature or a mere reflection of general intractability remains to be answered, our findings suggest that automatic exclusion of pharmacotherapy for patients with TLE who failed to achieve seizure freedom after receiving a third regimen may not be best and the choice of pharmacotherapy should vary depending on the prospects of the next therapeutic step.

Key words: epilepsy, pharmaco-resistance, juvenile myoclonic epilepsy, temporal lobe epilepsy

INTRODUCTION

Recent studies have demonstrated that first- and second-line antiepileptic drugs (AEDs), when appropriately chosen, can achieve seizure freedom in two-thirds of adult patients with drug-naïve epilepsy[1)2)]. On the other hand, those studies also emphasized that the seizure-free ratio in patients receiving a third-line AED was dramatically lower and that the prospects of successful fourth-line AED treatment are

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dim.

It is considered that different epileptic syndromes show different seizure prognoses, let alone intractable epileptic encephalopathies and, in contrast, self-remitting age-dependent focal epilepsies, such as BECT and Panayiotopoulos syndrome[3]. Although temporal lobe epilepsy is considered to be a challenge for pharmacotherapy[4], most studies agree that juvenile myoclonic epilepsy is relatively amenable to drug control[5][6]. Nevertheless, large scale cohort studies, especially with adult populations, have often failed to address this difference[7]. Furthermore, depending on the timing of therapeutic intervention, the alleged intractability of temporal lobe epilepsy varies greatly[1], as does the high level of pharmaco-responsiveness seen in juvenile myoclonic epilepsy[8]. In another study, meta-analysis failed to confirm the therapeutic superiority of valproate for generalized epilepsy, which may be because of blurred boundaries with other types of epilepsy[9]. Thus, direct comparisons of pharmaco-responsiveness among different epilepsy types have been strikingly scant so far.

In the present study, we examined the results of AED change for the purpose of seizure freedom in relation to seizure type.

METHODS

We retrospectively analyzed the records of patients over 15 years old who had been referred to the outpatient unit for epilepsy of Aichi Medical University between 2001 and 2013 and were followed for at least 1 year. Among 1396 patients who consulted with us during that time period, 947 were excluded from the present analysis because of insufficient follow-up period, a single unprovoked seizure, poor adherence to treatment, seizures secondary to drug or alcohol abuse, presence of psychogenic non-epileptic seizures, age-dependent focal epilepsy (e.g. BECT), epileptic encephalopathies (e.g. Lennox syndrome), or incomplete clinical records, especially insufficient description of pharmacotherapy prior to the referral. Consequently, the records of 468 patients were used. While 104 patients (22.2%) were newly diagnosed at our institution, the other 364 (77.8%) were referral cases. Interviews with the patient and family members, past medical records, and referral letters from the primary treating physician or discussions with them via telephone were the main sources of information. Patient background, medical history, current and previous AED use, achievement of seizure freedom, and results of examinations including surface electroencephalography and brain imaging were reviewed. Epileptic syndromes were defined according to the criteria of the 2010 International League Against Epilepsy[10], except for types of focal epilepsy. In this study, only patients who exhibited generalized bilateral jerks with either generalized tonic-clonic convulsions or generalized polyspike-wave-complexes on EEG starting after the age of 10 years were counted as juvenile myoclonic epilepsy (JME) cases. Using the 1989 classification as a reference[11], the presence of at least two of the following three features, complex partial seizures, auras typically encountered in cases of TLE, such as déjà vu, ictal fear, and epigastric aura, and temporal spikes on surface EEG were used as inclusion criteria for TLE[6]. Thus, the patients were classified into 3 groups; 153 in the TLE group, 33 in the JME group, and 263 in the non-J-non-T group (without either TLE or JME). Nineteen patients were excluded from the study because of difficulty with categorizing epilepsy type based on this trichotomy.

Any change of AED after initiation of pharmacotherapy, either substituted or added, was

counted as one change and regarded as one regimen, while dose change of the same drug was not counted.

Patients were considered seizure-free if they experienced no seizure for at least one year on unchanged treatment.

Statistical analysis was performed using a 2-sided Wilcoxon rank-sum test, Kruskal Wallis test, Fisher's exact test, and multi-variant analysis. Multi-variant analysis was performed using multiple regression analysis with focus on whether the number of AED regimens was related to the other clinical variables. McNemar's test was performed to compare longitudinal changes of seizure-free ratio for each regimen related to epilepsy type. Statistical calculations were performed using the SPSS for Windows software package (version 22).

RESULTS

1) Clinical background (Table 1). Both age at the initial AED therapy as well as at the last visit varied among the three groups ($p<0.044$ and $p<0.001$, respectively). At the initiation of AED therapy, the TLE group was older than the JME group ($p=0.020$), while age at the last visit was also older in the TLE and non-J-non-T groups as compared to the JME group ($p<0.001$; $p<0.001$ respectively), and also older in the TLE than in the non-J-non-T group ($p=0.007$). On the other hand, there were no significant differences among the groups with regard to age at onset, duration of medical treatment prior to the first visit to our hospital, or follow-up period after the first visit. Males outnumbered females in the non-J-non-T group.

2) AEDs (Table 2). The ratio of monotherapy at the final visit was the highest in the JME group (57.6%), followed by the non-J-non-T (41.4%) and TLE (22.9%) groups, and was significantly different among them ($p<0.001$). Also, the difference between the JME and TLE

Table 1. 449 subjects in three epileptic groups.

	JME ($n=33$)	non-J-non-T ($n=263$)	TLE ($n=153$)
Sex (male/female)*	14/19	167/96	75/78
Age at the last visit (yr.)*	28.7 (9.8)	37.2 (13.4)	41.5 (15.3)
Age at the start of medication*	16.5 (5.0)	21.0 (15.2)	24.3 (17.1)
Age at onset	14.5 (3.3)	18.8 (14.4)	20.9 (16.8)
Duration prior to the first visit (yr.)#	7.1 (9.7)	10.9 (11.5)	10.5 (11.1)
Follow-up period (yr.)	5.0 (3.4)	5.4 (3.2)	5.7 (3.5)

* Significant difference among the groups ($p<0.05$) examined by Kruskal-Wallis test or Fisher's exact test. Figures in the parenthesis means standard deviation.
# Interval between the first visit to us and the start of AEDs in other institutes.

Table 2. Characteristic of antiepileptic drugs use.

	JME	non-J-non-T	TLE
Monotherapy (%)* ($n=449$)	19/33 (57.6%)	109/263 (41.4%)	35/153 (22.9%)
Regimen numbers up to the last visit* ($n=449$)	2.1 (1.6)	3.2 (2.4)	4.1 (2.6)
Regimen numbers at the seizure freedom* ($n=209$)	1.6 (1.1)	2.2 (1.6)	2.9 (1.8)

* Significant difference among the groups ($p<0.01$) examined by Kruskal-Wallis test or Fisher's exact test. Figures in the parenthesis means standard deviation if it is not otherwise specified.

Table 3. Results of seizure outcomes.

	JME	non-J-non-T	TLE
Seizure free ratio at the 1st regimen ($n=449$)*	13 (39.4%)	61 (23.2%)**	10 (6.5%)**
Seizure free ratio at the 2nd regimen ($n=449$)*	4 (12.1%)	32 (12.2%)**	19 (12.4%)**
Seizure free ratio at the 3rd regimen ($n=449$)*	0 (0%)	20 (7.6%)**	12 (7.8%)**
Seizure free ratio at the 4th regimen ($n=449$)*	1 (3%)	9 (3.4%)	5 (3.3%)**
Final seisure free ratio ($n=449$)*	19 (57.6%)	135 (51.3%)	55 (35.9%)
Time interval between start of medication and seizure freedom, yr. ($n=197$)	7.1 (9.7)	10.2 (10.7)	8.9 (10.1)

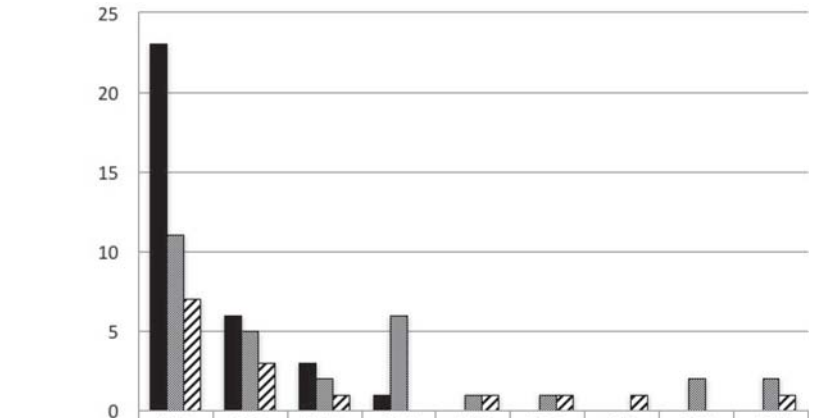
* Significant difference among the groups ($p<0.01$) examined by Kruskal-Wallis test or Fisher's exact test. Figures in the parenthesis means standard deviation if it is not otherwise specified. Yr stands for years.
** Significant difference among the regimens ($p<0.01$) examined by McNemar's test as longitudinal change in seizure-free ratio in relation to epilepsy type.

groups ($p<0.001$), and between the non-J-non-T and TLE groups ($p<0.001$) reached statistical significance. The number of regimens from the start of medication to the last visit was the greatest in the TLE group, followed by the non-J-non-T and JME groups, and was significantly different among the groups ($p<0.001$) as well as between each group (JME vs. TLE: $p<0.001$; JME vs. non-T-non-J: $p=0.003$; TLE vs. non-T-non-J; $p<0.001$). The same was also true for number of regimens at the time of achievement of seizure freedom (JME vs. TLE: $p<0.001$; JME vs. non-T-non-J: $p=0.05$; TLE vs. non-T-non-J: $p=0.002$)

3) Seizure outcome (Table 3). The seizure-free ratio during the first regimen showed a spectacular difference among the groups. That in the JME group was highest, followed by the non-J-non-T and TLE groups, with a statistically significant difference among them ($p<0.001$) and between any two groups (JME vs. TLE; $p<0.001$; JME vs. non-J-non-T: $p=0.009$; TLE vs. non-J-non-T: $p<0.001$). The discrepancy for seizure-free ratio was decreased at the last visit, though the difference remained statistically significant among the groups ($p=0.004$), and between the JME and TLE groups ($p=0.03$), as well as between the TLE and non-J-non-T groups ($p=0.030$) until the last visit. There was no difference among the groups in regard to time needed to achieve seizure freedom.

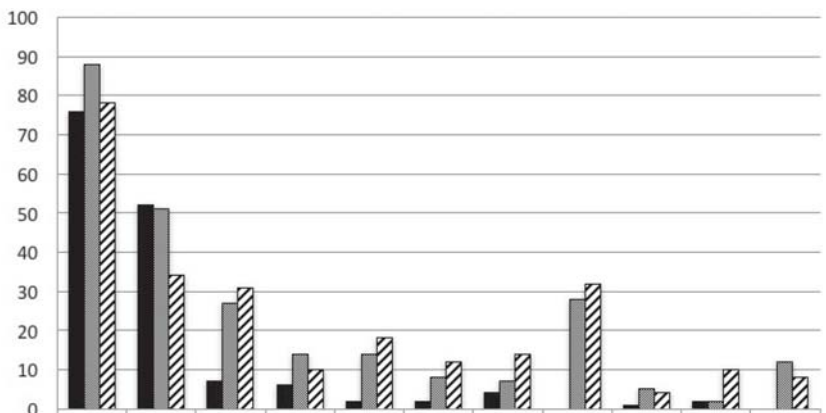
The main result of the present study was longitudinal change in seizure-free ratio in relation to epilepsy type. In the TLE group, the changes in seizure-free ratio between the first and second regimen ($p<0.001$), between the second and third regimen ($p<0.001$), and between the third and fourth regimen ($p<0.001$) were significantly different. In the non-J-non-T group as well, there was a statistically significant difference between the first and second regimen ($p<0.001$), and between the second and third regimen ($p<0.001$), though not between the third and fourth regimen. In contrast, there were no significant differences found between regimens in the JME group in regard to longitudinal change of seizure-free ratio.

In the JME group (Figure 1), the most frequently prescribed AED through the first, second, and third regimens was valproate, with ratios of 69.7%, 68.8%, and 87.5%, respectively. In the TLE group (Figure 2), the most frequently prescribed AED was carbamazepine through the first, second, and third regimens, with those ratios steadily increasing from 49.7



	VPA	CBZ	PHT	ZNS	TPM	LTG	CLB	CZP	LEV
1st regimen	23	6	3	1	0	0	0	0	0
2nd regimen	11	5	2	6	1	1	0	2	2
3rd regimen	7	3	1	0	1	1	1	0	1

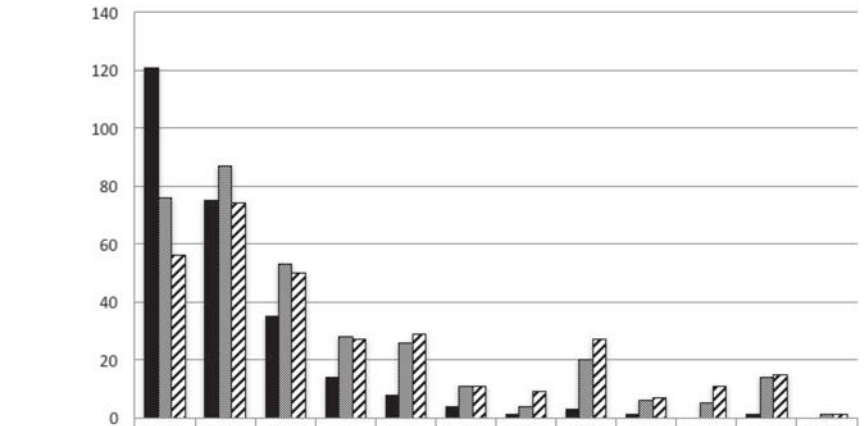
Figure 1. AED contents in JME.
In the JME group, the most frequently prescribed AED through the first, second, and third regimens was valproate, with ratios of 69.7%, 68.8%, and 87.5%, respectively.
VPA: Valproate CBZ: Carbamazepine PHT: Phenytoin ZNS: Zonisamide TPM: Topiramate LTG: Lamotrigine CLB: Clobazam CZP: Clonazepam LEV: Levetiracetam



	CBZ	VPA	PHT	PB	ZNS	TPM	LTG	CLB	CZP	GBP	LEV
1st regimen	76	52	7	6	2	2	4	0	1	2	0
2nd regimen	88	51	27	14	14	8	7	28	5	2	12
3rd regimen	78	34	31	10	18	12	14	32	4	10	8

Figure 2. AED contents in TLE.
In the TLE group, the most frequently prescribed AED was carbamazepine through the first, second, and third regimens, with those ratios steadily increasing from 49.7%, to 63.3% and 71.8%, respectively.
CBZ: Carbamazepine VPA: Valproate PHT: Phenytoin PB: Phenobarbital ZNS: Zonisamide TPM: Topiramate LTG: Lamotrigine CLB: Clobazam CZP: Clonazepam GBP: Gabapentin LEV: Levetiracetam

%, to 63.3% and 71.8%, respectively. For the first regimen, valproate was given to 34.6% in the TLE group and 46.7% in the non-T-non-J-group. When analysis was limited to females,



	VPA	CBZ	PHT	PB	ZNS	TPM	LTG	CLB	CZP	GBP	LEV	PRM
1st regimen	121	75	35	14	8	4	1	3	1	0	1	0
2nd regimen	76	87	53	28	26	11	4	20	6	5	14	1
3rd regimen	56	74	50	27	29	11	9	27	7	11	15	1

Figure 3. AED contents in non-J-non-T.
For the first regimen, valproate was given to 34.6% in the TLE group and 46.7% in the non-T-non-J-group. When analysis was limited to females, valproate was prescribed as the first regimen to 34.6% and 39.5%, respectively.
VPA: Valproate CBZ: Carbamazepine PHT: Phenytoin PB: Phenobarbital ZNS: Zonisamide TPM: Topiramate LTG: Lamotrigine CLB: Clobazam CZP: Clonazepam GBP: Gabapentin LEV: Levetiracetam PRM: Primidone

Table 4. Multiple regression analysis influencing final number of regimens.

	Mean	*t* ratio	*p* value
Epipelsy type			
JME	1.9 (1.3)	0.958	0.05
TLE*	4.0 (2.5)	2.586	<0.001
non-J-non-T*	3.2 (2.5)	1.93	<0.001
Sex	3.3 (2.5)	0.194	0.21
Age at onset	3.4 (2.5)	0.041	0.088
Age at start of medication*	3.4 (2.5)	−0.081	<0.001
Age at last visit*	3.4 (2.5)	0.036	<0.001
Seizure outcome*	4.2 (2.5)	1.495	<0.001

* Earlier start of medication ($p<0.001$), older age at the last examination ($p<0.001$), and failure to achieve a seizure-free state ($p<0.001$) understandably contributed significantly to the final number of regimens, as did epilepsy type ($p=0.0013$). Figures in the parenthesis means standard deviation if it is not otherwise specified.

valproate was prescribed as the first regimen to 34.6% and 39.5%, respectively (Figure 3).

4) Multiple regression analysis. Multiple regression analysis was performed with the final number of regimens as the dependent variable, while the independent variables were type of epilepsy (JME, TLE, others), sex, age at the last visit, age at the start of medication, age at epilepsy onset, and achievement of seizure freedom (Table 4). Age at onset ($p=0.088$) and sex ($p=0.21$) were shown to be unrelated to the final number of regimens, whereas earlier start of medication ($p<0.001$), older age at the last examination ($p<0.001$), and failure to achieve a

seizure-free state ($p<0.001$) understandably contributed significantly to the final number of regimens, as did epilepsy type ($p=0.0013$).

DISCUSSION

The present study revealed that even fourth-line AED treatment significantly increased the seizure-free ratio in patients with TLE, while the initial AED trial was most likely to be successful in JME patients. Although the seizure-free ratio in the JME group in response to the first regimen was slightly greater than that seen in epilepsy patients as a whole, the striking discrepancy for the first regimen among epilepsy types was mainly because of the low response rate of the TLE group (6.5%) during the first regimen, as the average ratio of seizure freedom in response to the initial medication has been reported to range from 40% to 50%[7]. On the other hand, it should be noted that 2.5 times more patients achieved seizure freedom after the second regimen in comparison with the first-line treatment in the TLE group. This is especially noteworthy in consideration of the assumption that only half of the patients in a general population with epilepsy will achieve seizure freedom after the second regimen in comparison with the first.

The tendency of late remission in the TLE group agrees with a previous study, which stressed focal epilepsy as a factor promoting the delay of remission[12]. In our study, the fourth regimen in the non-J-non-T group, which occupied the largest portion of the study sample, failed to increase the seizure-free rate, in agreement with previous large cohort studies[5], whereas our findings demonstrate that fourth-line treatment is worth attempting for patients with TLE.

Another possible explanation for the strikingly low responsiveness of the present TLE patients to the first regimen may have been because of the lack of differential choice of AEDs in the primary care setting. In the current cohort, carbamazepine was most often prescribed for each of the regimens in the TLE group, while valproate was the most common in the JME group. On the other hand, the proportion of patients who used carbamazepine increased steadily in the TLE group, which may explain the increased pharmaco-responsiveness in those patients. In contrast, the proportion of patients who used valproate did not increase so dramatically in the JME group. In Japan, primary care givers are reluctant to prescribe carbamazepine, because of potentially lethal skin rashes, which may have widened the discrepancy of pharmaco-responsiveness as a function of epilepsy type, as monotherapy with the most recently marketed AEDs, such as levetiracetam and lamotrigine, was not covered by national health insurance until recently.

Our results strongly support the suggestion made recently by Tomson in regard to CEA-ILAE that valproate should be avoided in women of childbearing age with focal epilepsy[13]. That study also emphasized the need for intensive discussion and shared decision-making with patients and families after careful risk-benefit assessment for patients with JME. In the current study, 34.6% in the TLE group and 46.7% in the non-T-non-J group were given valproate as the first regimen, and the ratio remained nearly the same when the analysis was limited to females. Our results confirmed the importance of differential diagnosis of epilepsy type when choosing an AED, even in this era of broad spectrum AEDs, and also revealed the extensive use of valproate as the initial AED even in cases of focal epilepsy, which emphasizes the significance of Tomson's recommendation. Valproate is included in the group of broad

spectrum type AEDs, which is officially recommended as a treatment option for focal epilepsy in treatment guidelines not only in Japan but in other countries as well[14].

At the time of the last visit, that is, after adjustment to a supposedly optimal AED after more than 1 year of follow-up examinations, the difference in pharmaco-responsiveness remained statistically significant, though it was substantially diminished. Even after the initial failure of pharmacotherapy, up to 35% of TLE patients are still expected to achieve seizure freedom. Indeed, even though this figure is lower than expected for other types of epilepsy, it is promising enough to vigorously pursue such a treatment plan.

LIMITATION

Since our retrospective study was performed with large percentage of referral cases (77.8%), low responsiveness of the TLE patients to the initial pharmacotherapy may have been because of the inappropriate choice of AEDs in the primary settings. Result might be affected if this study is limited to the patients with newly diagnosed as epilepsy in our outpatient unit for epilepsy.

CONCLUSION

Although whether this striking trend of late remission in the TLE group was intrinsic in nature or a mere reflection of general intractability remains to be answered, our findings suggest that automatic exclusion of pharmacotherapy for patients with TLE who failed to achieve seizure freedom after receiving a third regimen may not be best and the choice of pharmacotherapy should vary depending on the prospects of the next therapeutic step. Patients with hippocampal sclerosis or a circumscribed tumor may be preferably referred to a surgical center following failure of the second regimen, if the AED is appropriately chosen[15][16]. In contrast, it may be prudent to attempt a fourth regimen in patients with MRI-negative TLE[4] before dispatching them to a surgical center. In those cases, it is important to cautiously consider both risks and benefits before giving up pharmacotherapy, because late remission may be as good as successful surgical intervention. Further studies must be undertaken in the spirit of understanding pharmacotherapy for intractable epilepsy.

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