



International Journal of Pharmacology

ISSN 1811-7775

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Research Article

Utilization of Antiepileptic Drugs on Monotherapy and Polytherapy for Children at Shanghai in China

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Abstract

Objectives: It was well known that the utilizations of antiepileptic drugs had been shown in many countries, such as Italy, Netherlands, Dutch and so on. However, those in China were rarely disappeared. In this study, the AEDs using pattern in clinic for children at Shanghai of China were studied. Moreover, the application of monotherapy and polytherapy of AEDs was analyzed to assess whether drug mono and polytherapy are rational or not. **Methods:** In this study, 8160 prescriptions of total 1,483,061 children aged 0-18 years in the Children's Hospital of Fudan university on the diagnosis of epilepsy were retrieved from July, 2014 to October, 2015. Prescribing pattern of AEDs and the individual AEDs applied to monotherapy and polytherapy on using rate and dosage were analyzed. Besides, the utilization of valproic acid (VPA), levetiracetam (LEV) and topiramate (TPM) prescribed to different ages of children were covered. **Results:** Children aged from 2-11 years were the most frequency in the prescriptions with 74.07%. The VPA solution, LEV tablet, oxcarbazepine (OX) tablet and TPM were in the highest frequency used both in monotherapy and polytherapy. Meanwhile, proportion of older and newer AEDs on polytherapy arrived at 59.83 and 53.84%, which was higher than those of monotherapy with 18.67 and 39.63%. Furthermore, the dosage was increased from 9.50 ± 0.17 to 11.49 ± 0.34 mL in VPA group, from 4.79 ± 0.1 to 5.61 ± 0.19 mL in LEV group and from 59.45 ± 2.46 to 77.34 ± 3.06 mg in TPM with the number of medication added on polytherapy, which were significantly higher than monotherapy. **Conclusion:** The usage of newer AEDs in children was all-too-frequency at Shanghai of China, while polytherapy was most commonly used in Chinese children and certain different dose between monotherapy and polytherapy was found in VPA, LEV and TPM.

Key words: Monotherapy, polytherapy, antiepileptic drugs, VPA, TPM, AEDs

Received: March 05, 2016

Accepted: March 29, 2016

Published: June 15, 2016

Citation: Yan Wang and Zhiping Li, 2016. Utilization of antiepileptic drugs on monotherapy and polytherapy for children at Shanghai in China. *Int. J. Pharmacol.*, 12: 496-504.

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Competing Interest: The authors have declared that no competing interest exists.

Data Availability: All relevant data are within the paper and its supporting information files.

INTRODUCTION

Drug utilization study had been defined by World Health Organization as, marketing, distribution, prescription and use of drugs in society with special emphasis on the resulting medical, social and economic consequence. The ultimate goal of drug utilization study must be to assess whether drug therapy is rational or not¹. Pharmacotherapy is the principle treatment for epilepsy. In recent years, many studies had revealed the utilization of AEDs in UK, Italy, Netherlands, Norway, Singapore and Korea²⁻⁵. However, rare study was shown in China.

It was well known that 20-30% of patients still failed to monotherapy and about 20% of refractory of epilepsy tended to accept the polytherapy^{6,7}. Polytherapy was a pharmacotherapy that prescribing more than two AEDs. Though, many reports showed that there was no effect on the concentrations of AEDs combined with LEV and TPM, the risk of side effects on polytherapy still increased without doubt⁸⁻¹⁰. Studies showed that 56% of patients used more than one AED in Norway¹¹. Polytherapy was observed in 49.7% of patient in one of hospital of Korea¹². However, the using rate and using dosage of AEDs on polytherapy were not known in China.

In this study, the AEDs using pattern in clinic for children at Shanghai of China were studied. Moreover, the application of monotherapy and polytherapy of AEDs was analyzed to assess whether polytherapy are rational or not.

MATERIALS AND METHODS

Data source and study population: Total of 1,483,061 of out-patients from 1st July, 2014 to 31st October, 2015 were retrieved in the electronic database of Children's Hospital of Fudan university. Then, the prescriptions with the diagnosis of epilepsy and dispensing data were selected in this study.

The study population was defined as patients aged 0 day to 18 years who were diagnosed by epilepsy. The VPA, clonazepam (CZP), carbamazepine (CBZ) and phenobarbital (PB) were identified as the older AEDs, while, the LEV, OXC, TPM and lamotrigine (LTG) as the newer one on the basis of market availability before versus after 1991¹³. The daily dose of VPA, LEV, OXC and TPM used in each age of children were displayed in details.

Groups: The dispensing data was divided into four groups, namely, the mono-medication group, the double-medication group, triple-medication group and multi-medication group which contained one, two, three and more than three medications in one prescription, respectively.

The ages were departed into four periods, the first period contains the 0-28 days, followed by 28 days to 23 months, 2-11 and 12-18 years.

Data analysis: Firstly, demographic data on ages and gender was analyzed and the rate was calculated by dividing to the total patient in this study (8160). In order to recognize the use of older and newer AEDs in monotherapy and polytherapy, the proportion was also computed.

Daily dosage of individual AED was calculated and data was expressed as the Mean±SE. Then, Bonferroni test compare all pairs of columns was applied in analysis of different dosage between monotherapy and polytherapy through using Prism 5 software, differences were considered statistically significant at p<0.05.

RESULTS

Demographic data: There were 8160 prescriptions of total 1,483,061 children included in this study. It was the number of male that was about 1.57 times than that of the female. The majority of children were on the age of 2-11 years (74.07%). 53.16% of total children were prescribed to monotherapy and the rest were on polytherapy. Age of 2-11 years was the majority on polytherapy, where 51.31% of children were applied for more than three AEDs (Table 1).

Utilization pattern of older and newer AEDs: The most commonly prescribed AED was VPA, an older AED, whose rate reached to 50.17% (4094/8160), followed by the LEV (30.85%, 2517/8160) and OXC (30.22%, 2466/8160). The CBZ, PB and CZP showed lower rate at 1.10% (76/8160), 0.93% (76/8160) and 6.29% (531/8160), respectively. The total amount of newer AEDs containing LEV, OXC, TPM and LTG was 6968, higher than that of older AEDs (4773) including VPA, CZP, CBZ and PB (Fig. 1a). Rate of both

Table 1: Demographic data of children

Groups	>28 days~			
	0~28 days	23 months	2~11 years	12~18 years
Mono-medication				
Male	0	191 (2.34%)	2002 (24.53%)	492 (6.03%)
Female	0	138 (1.69%)	1251 (15.33%)	264 (3.24%)
Double-medication				
Male	0	94 (1.15%)	797 (9.77%)	245 (3.00%)
Female	0	55 (0.67%)	621 (7.61%)	149 (1.83%)
Triple-medication				
Male	0	47 (0.58%)	625 (7.66%)	207 (2.54%)
Female	0	41 (0.50%)	409 (5.01%)	81 (0.99%)
Multi-medication				
Male	0	21 (0.26%)	215 (2.63%)	54 (0.66%)
Female	0	15 (0.18%)	124 (1.52%)	22 (0.27%)

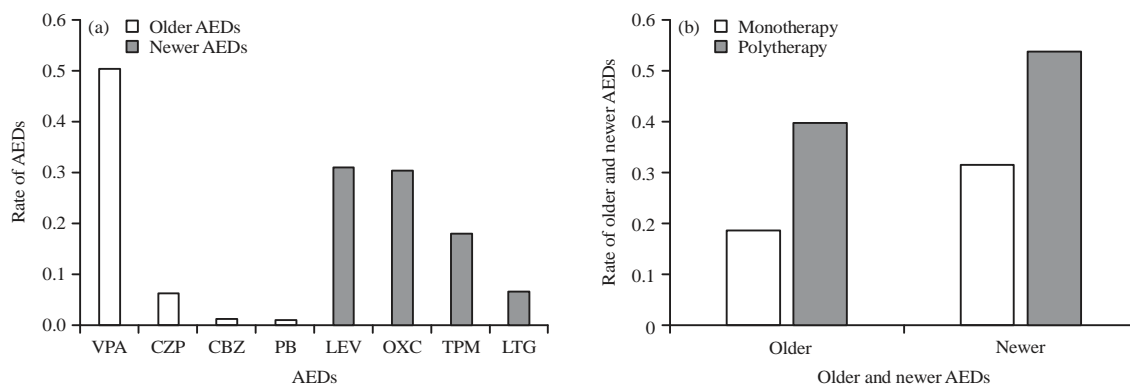


Fig. 1(a-b): Older and newer AEDs used in prescriptions. Results are presented as the rate divided by the total count of prescriptions (8160), (a) Rate of individual AED and (b) Rate of older and newer AED on monotherapy and polytherapy

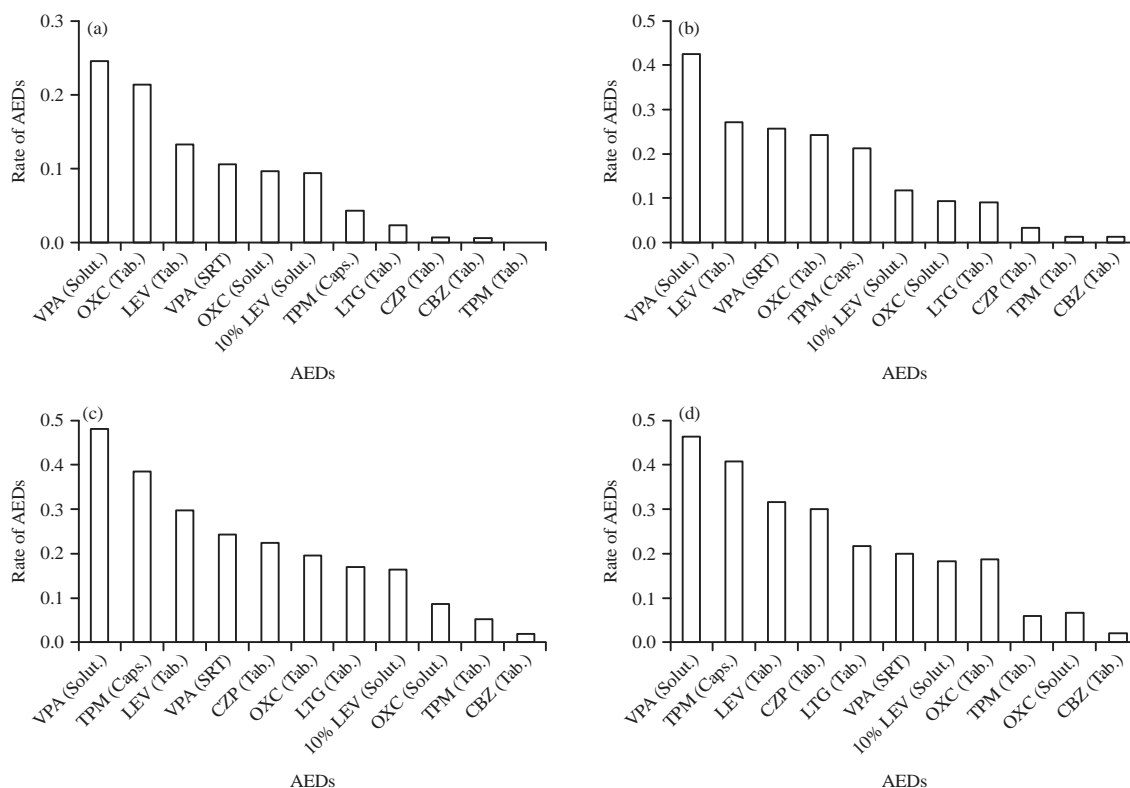


Fig. 2(a-d): Individual utilization of AED on monotherapy and polytherapy. Results were presented as the rate divided by the total count of prescriptions (8160), (a) Mono-medication group, (b) Double-medication group, (c) Triple-medication group and (d) Multi-medication group

older and newer AEDs on polytherapy (39.83 and 53.84%) were higher than monotherapy (18.66 and 31.56%) (Fig. 1b).

Utilization of AED on monotherapy and polytherapy: It was showed that VPA solution, OXC tablet, LEV tablet and TPM capsular were widely used on both monotherapy and polytherapy. The percentage of VPA solution divided by total amount was 24.57, 42.73, 48.44 and 46.34% in

mono-medication, double-medication, triple-medication and multi-medication, which suggested that the utilization of VPA on polytherapy was higher than monotherapy. Percentage of LEV tablet got a slight increase from 13.35-31.49%, while, TPM and CZP showed a rapid increase with the number of combination agents added from 4.39-40.22% and from 0.71-29.89%, respectively. While the proportion of OXC tablet revealed a slight decrease from 21.35-18.85% (Fig. 2a-d).

Table 2: Dosage of individual of AED in mono-medication, double-medication, triple-medication and multi-medication group

AEDs	Mono-medication	Double-medication	Triple-medication	Multi-medication
VPA (mL)	9.50±0.17	10.63±0.15 ^a	11.61±0.17 ^{a,b}	11.49±0.34 ^a
LEV (mL)	4.79±0.11	5.78±0.22 ^a	5.60±0.15 ^a	5.61±0.19 ^a
TPM (mg)	59.45±2.46	68.50±1.60	91.07±2.12 ^{a,b}	77.34±3.06 ^{a,c}
OXC (g)	0.86±0.10	0.80±0.015	0.89±0.021	0.88±0.041
LTG (mg)	97.98±3.44	107.40±3.32	109.70±2.93	110.00±4.92
CZP (mg)	1.48±0.20	1.33±0.13	1.76±0.32	1.87±0.11
CBZ (g)	0.51±0.034	0.64±0.045	0.61±0.051	0.83±0.13

^{a,b,c}Marked when the analysis was statistical compared to the mono-medication, double-medication and tri-medication, respectively (p<0.05). Data was shown as Mean±SE

Table 3: Dosage of VPA, LEV and TPM applied to monotherapy and polytherapy with different period age

AEDs	Mono-medication	Double-medication	Triple-medication	Multi-medication
VPA (mL)				
28 days-23 months	5.53±1.45	6.17±1.75	7.06±2.54 ^{1,2}	6.89±2.15
2-3 years	7.26±2.14 ^a	8.81±2.75 ^{a,1}	9.02±2.65 ^{a,1}	8.11±2.83
4-11 years	10.70±5.55 ^{a,b}	12.00±4.09 ^{a,b,1}	13.07±4.46 ^{a,b,1,2}	12.32±4.32 ^{a,1}
12-18 years	12.54±8.24 ^{a,b}	11.87±7.79 ^{a,b}	13.61±5.13 ^a	19.43±5.75 ^a
LEV (mL)				
28 days-23 months	3.20±1.37	4.60±5.95	3.55±1.14	3.78±1.12
2-3 years	4.30±1.68	4.90±1.82 ¹	4.58±1.89	5.09±1.33
4-11 years	6.23±2.76	7.21±2.50 ^a	7.38±2.51 ^a	6.95±2.60 ^a
12-18 years	0.00±0.00	12.00±0.00	10.00±0.00	0.00±0.00
TPM (mg)				
28 days-23 months	36.37±23.93	37.74±18.54	51.77±35.88	45.09±30.24
2-3 years	49.65±20.10	60.40±24.11	64.45±25.00	64.03±21.36
4-11 years	72.35±31.26 ^a	75.72±32.44 ^a	89.71±43.17 ^{a,b,1,2}	78.84±35.92 ^a
12-18 years	98.75±52.19 ^{a,b}	99.61±32.86 ^{a,b}	144.30±70.88 ^{a,b,c,1,2}	114.00±63.77 ^{a,b,c}

^{a,b,c}Marked when the analysis was statistical compared with the 28 days to 23 months, 2-3 and 4-11 years, respectively (p<0.05), ^{1,2}Statistical analysis compared with mono-medication and double-medication (p<0.05). Data was shown as Mean±SE

Dosage of individual AED on monotherapy versus polytherapy:

The dosage of VPA and LEV was increased with the number of medication added from 9.50±0.17 to 11.49±0.34 mL and from 4.79±0.11 to 5.61±0.19 mL, respectively. Data in double, triple and multi-medication were significantly higher than those in mono-medication. The highest dose of TPM was 91.07±2.12 mg in triple-medication, while, dosage both in triple-medication and multi-medication were larger compared with mono-medication. While, in LTG, CZP and CBZ, it seemed to reveal a slight increase, but no statistical difference between monotherapy and polytherapy was found. No change was seen in OXC among four groups (Table 2).

Dose of VPA, LEV and TPM in different ages: The range of dosage of VPA-solution was widespread from 0.3-52 mL on monotherapy and polytherapy (Fig. 3a-d). It increased with ages went up and dosage in 12-18 years group was about two times than that of 28 days to 23 months in mono-medication. Similar trend was seen in double-medication, triple-medication and multi-medication. Besides, the dosage of 28 days to 23 months, 2-3 and 4-11 years in

triple-medication was higher than those of mono-medication, statistically. Apparent difference between mono-medication and multi-medication was founded in children aged 4-11 and 12-18 years (Table 3).

Distributions of 10% LEV solution and LEV tablet were different. Rate of 10% LEV solution reached to 22.98, 38.13 and 38.89% at the age of 28 days to 23 months, 2-3 and 4-11 years, respectively. Only two children aged from 12-18 years used 10% LEV solution. While, the rate of LEV tablet was focused at the children aged from 4-11 years (67.67%). Further study on the dosage distribution of 10% LEV solution showed that the range of dosage of LEV solution was spread from 0.6-41.0 mL (Fig. 4a-d). It was higher in the 4-11 years group than those in 28 days to 23 months, however, only the rate of children aged from 2-3 years in double-medication showed a significant higher compared with mono-medication (Table 3).

The range of TPM was concentrated in several main doses (Fig. 5a-d). It was showed that ages from 4-18 years suffered higher dosage of TPM than the younger one, which suggested that dosage was increased with the age of children added. The TPM showed an increase in 4-18 years on tri-medication compared to mono-medication and double-medication.

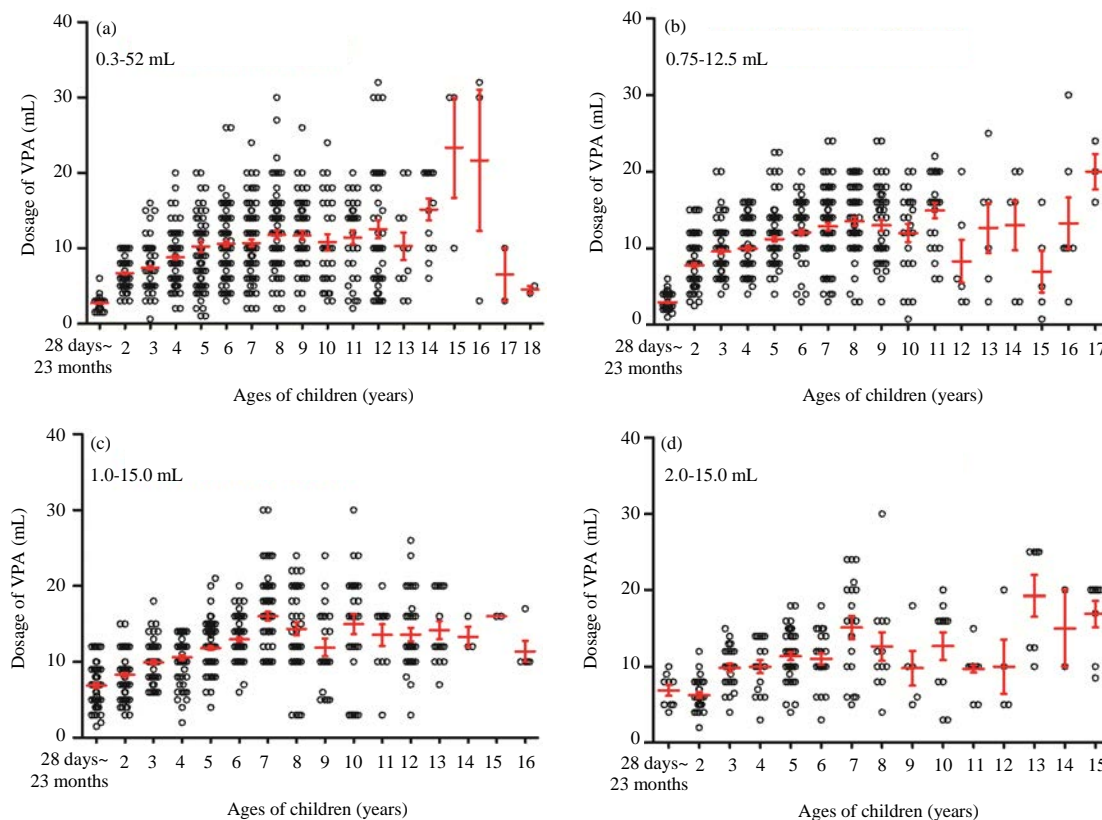


Fig. 3(a-d): Distribution of age on the dosage of VPA. Black circle plot represented the individual dosage of VPA (mL). Results were shown as Mean \pm SE with the red line, (a) Mono-medication group, (b) Double-medication group, (c) Triple-medication group and (d) Multi-medication group

DISCUSSION

In this study, it suggested that the usage of newer AEDs was all-too-frequency, the commonly used drugs on polytherapy were different from monotherapy and the dosage of VPA, TPM and LEV showed a significant increase on polytherapy than on monotherapy.

It was denoted that the utilization of newer AEDs at Shanghai of China was prevalent in childhood epilepsy patients, reached to 53.84%, which was less than those of Korea where the use of newer AEDs increased rapidly from 53.4% in 2001 to 74.3% in 2012¹². While, it showed a slight higher than those in Norway, Italy and UK in 2005¹⁴⁻¹⁶. In the second place, the application of both older AEDs and newer AEDs on polytherapy were higher than monotherapy, which was to the contrary in Anderson M's and van de Vrie-Hoekstra NW's research^{10,16}. Safety and better tolerated might account for higher utilization of newer AEDs. It was reported that patients taking newer AEDs report ≥ 1 adverse events which were much less frequently than patients on older AEDs.

Moreover, the older AEDs were associated with a greater likelihood of potential drug-drug interactions than newer AEDs¹⁷⁻¹⁹.

Total of 46.84% of children suffered from polytherapy, while, in India only 20% of cases were on polytherapy and the rate was 22.8% in the Netherlands and 27% in the USA from 1997-2005^{1,16,20}. It was found that VPA was the most commonly used AEDs in this study, followed by LEV and OXC, while, CBZ was the lowest one, which was different from the Moran N.F.'s research where VPA, CBZ and LTG were mostly used from 1997-2009¹⁵.

It was shown that, VPA was commonly used not only on polytherapy but on monotherapy, evenly higher on polytherapy, which differ from the Netherlands where VPA, CBZ and other old AEDs were prescribed more often in monotherapy than in combination therapy¹⁶.

The VPA, which might affect the function of GABA_A receptors and NMDA receptors, was recommended to the treatment for many types of epilepsy¹. It was higher dosage used in double, triple and multi-medication than in

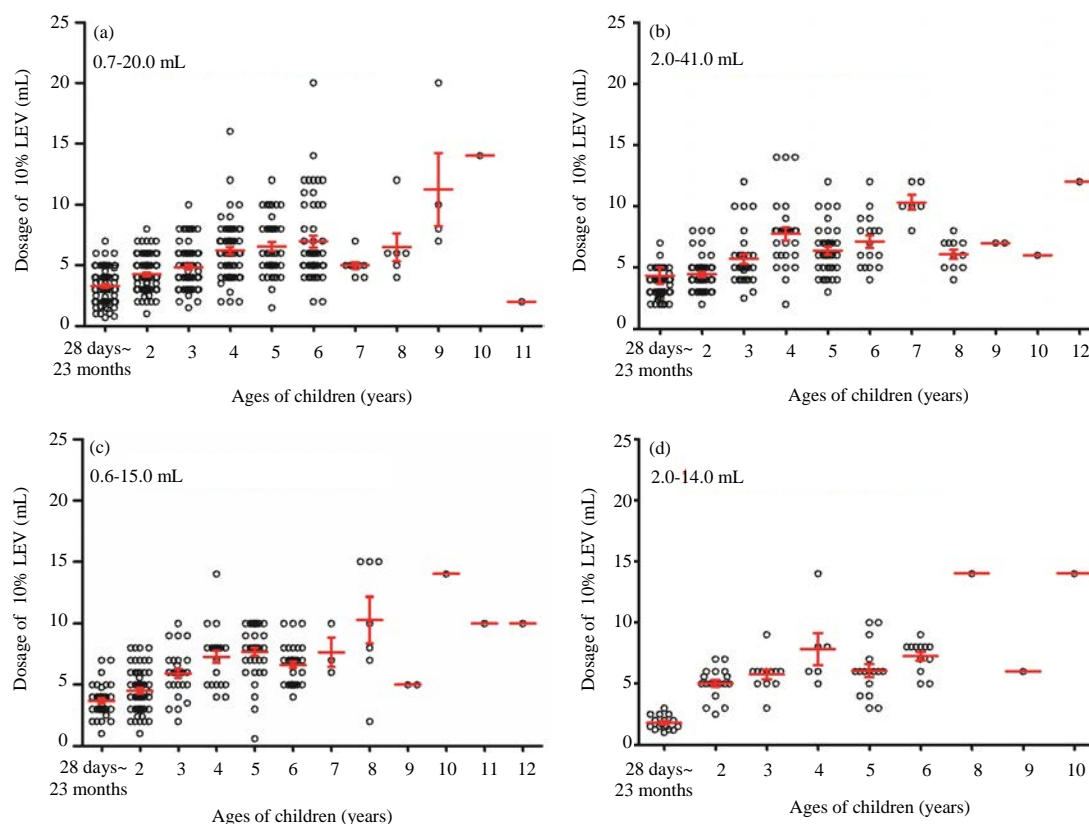


Fig. 4(a-d): Distribution of age on the dosage of 10% LEV. Black circle plot represented the individual dosage of 10% LEV (mL). Results also were shown as Mean \pm SE with the red line, (a) Mono-medication group, (b) Double-medication group, (c) Triple-medication group and (d) Multi-medication group

monotherapy in this investigation, which might owe to the fail therapy on mono-medication, consequently, polytherapy with a higher dose seemed be a better option.

The TPM was also got a higher dose on triple-medication than monotherapy, which demonstrated that TPM might consider as a treatment option before moving onto surgical. However, study had shown that TPM was associated with better cognitive outcome on monotherapy than treatment in polytherapy²¹.

As for OXC and LTG no distinction was found in this study, which reflected that those might be the adjunctive on polytherapy.

It was well established that the plasma concentration of VPA was irregular among individuals, while the range of dosage of VPA was wide spread from 0.3-52 mL from 28 days to 18 years, in this analysis. Research had reported that too higher dosage used for children meant higher risk when combined with TPM, which reminded that monitoring should be necessary and much cautions should be taken for children for some side effect such as nausea, epigastria pain and tremor¹.

The TPM, as a first recommended agent for the treatment of certain refractory epilepsy syndromes such as Lennox-Gastaut and West syndromes, was believed to be effective for seizure reduction with little serious side effect in children aged over 4 years²². The Proportion of children less than 2 years in this studies arrived at 12.99%. Korean study had shown that TPM had the same long-term retention rate in children under the age of 2 years and no serious side effect²², whether it was safe for children under 2 years needed much more further experiments.

The LEV is approved as an initial monotherapy only in children ≥ 16 years as well as adjunctive therapy in children ≥ 1 month with partial epilepsy and in children ≥ 6 years with primary generalized seizure. Many researches have showed that LEV can be used as an effective and safe added-on treatment in children^{23,24}. In this study, about 52.28% of total LEV was used by children less than 16 years on monotherapy. However, studies on collecting of 32 studies on LEV monotherapy in children showed that it was insufficient to confirm that LEV was effective as initial monotherapy for different types of seizures²⁵.

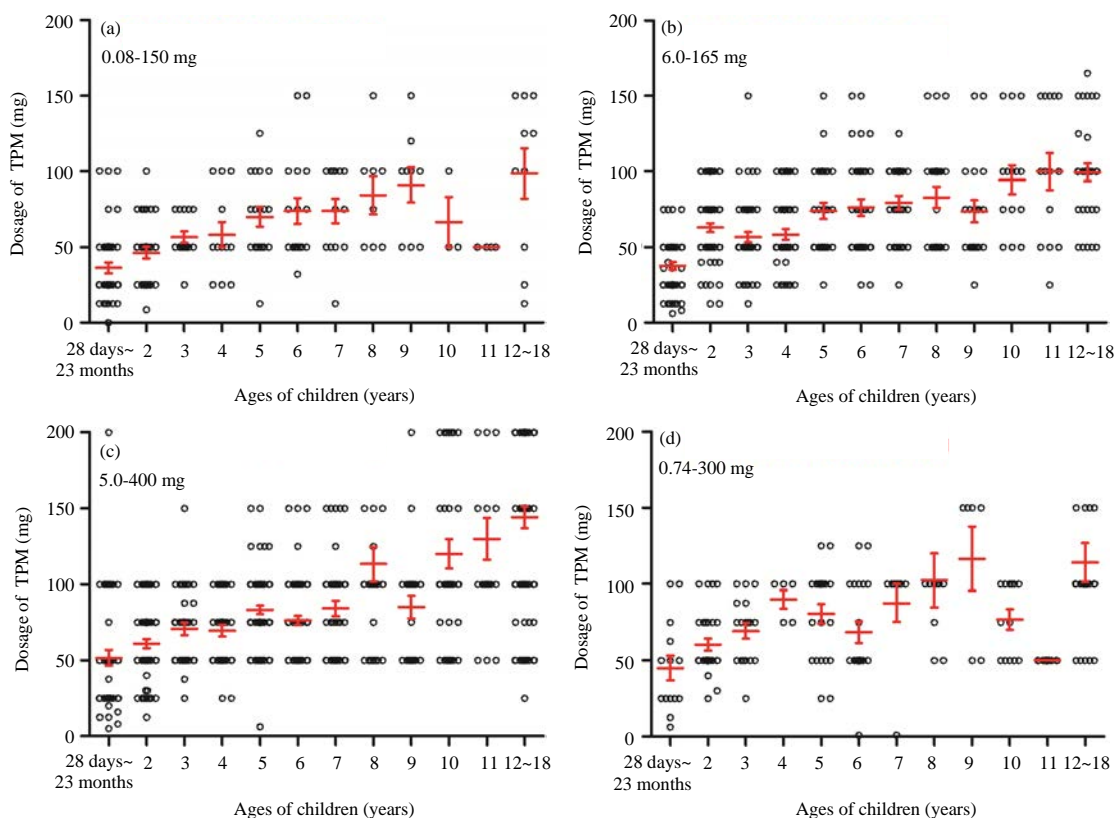


Fig. 5(a-d): Distribution of age on the dosage of TPM. Black circle plot represented the individual dosage of TPM (mg). Results were shown as Mean \pm SE with the red line, (a) Mono-medication group, (b) Double-medication group, (c) Triple-medication group and (d) Multi-medication group

In the total of patients, 53.16% of children were prescribed to monotherapy and the rest of 46.84% were suffered by polytherapy, of which 51.31% of children were applied for more than three AEDs, which suggested that polytherapy was commonly used in children epilepsy. The minimize dosage on monotherapy of each age was lower than those recommended in drug labels, which might account for the inefficient monotherapy and course a higher frequent utilization on polytherapy. Other reason of the commonly use of polytherapy was contributed to the multi-drugs resistance, defined by the inefficient usage of more than two AEDs. It was revealed that about 20~30% of epilepsy failed to drug therapy and 70% of patients who failed to the first AEDs tend to pharmacological resistance²⁶. Nevertheless, the mechanism was still unknown. Studies have found the closely relationship between P-glycoprotein (P-gp) which could exclude AEDs out of the tissue in brain and multi-drugs resistance^{27,28}. Human owning mutations of MDR 1 coding for P-gp in human have higher concentration of AEDs in tissue of brain as well²⁹. Further clinical adult study had showed that combine verapamil with AEDs could increase the blood concentration and cause efficient therapy than one who never applied

verapamil, even applied to children³⁰⁻³². But how the verapamil improve the therapy and whether it could be used to clinical therapy to inhibit the multi-drug resistant which might consequently led to higher frequency of polytherapy reserved further experiments.

Some limitations included in this study. The deficiency of concrete was diagnosed firstly. Diagnosis of only epilepsy in prescriptions showed difficult to identify the type of epilepsy. Besides, the lack of the weight of children made it difficult to evaluate whether the dosage of AEDs used for children was accurate or not.

CONCLUSION

The usage of newer AEDs in children was all-too-frequency and polytherapy was most commonly used in AEDs at Shanghai of Chinese. There was certain different dose between monotherapy and polytherapy in VPA, LEV and TPM. Much care should be taken when applied to AED and further studies needed to solve the multi-drug resistance for giving some more accurate treatment for children.

ACKNOWLEDGMENTS

Thanks to Qin Li and Jinmiao Lu for modification to this study and thanks to Rui Li and Feng Zheng for the collecting of data.

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