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Reinvestigation and Reduction of Polytherapy in Children With Chronic Seizures

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From October 2001 to October 2003, the authors reviewed all patients with chronic seizures taking antiepileptic drugs for more than 2 years with follow-up at the pediatric neurological clinic. They identified 31 patients who were using 3 or more drugs. Twenty-nine patients agreed to undergo a drug reduction and readjustment. The authors spent a mean period of 14.1 months to either purely reduce the numbers of drugs or introduce a new drug (rational polytherapy) plus removal of some drugs to achieve the end goal of a maximum of 2 or 3 drugs (if necessary). Seizure control in 96.6% of patients (28 of 29 patients) did not worsen after the readjustment and reduction of the antiepileptic drugs. Instead, 65.5% (19 of 29 patients) got better, and 37.9% (11 of 29) were seizure free. The number of antiepileptic drugs before and after adjusting was 3.6 (range, 3-6) to 1.9 (4 monotherapy, 22 duotheray, and 2 triple drugs). The most common combined therapies were sodium valproate/lamotrigine (n = 10) and carbamazepine/topiramate (n = 5). Although the results could be possibly attributed to the spontaneous remission of the seizures, it was still shown that those patients were overtreated. Serial addition to 3 or more antiepileptic drugs is less likely to lead to seizure freedom for patients with difficult-to-treat epilepsy. On the contrary, polytherapy and some antiepileptic drugs could aggravate seizures. Certain combinations of antiepileptic drugs (rational polytherapy) offer better efficacy to control seizures.

Keywords: refractory epilepsy; overtreatment; rational polytherapy

For patients with documented epilepsy, anticonvulsant drugs are the mainstay of treatment. Modern outcome studies have demonstrated that 60% to 70% of patients with newly diagnosed epilepsy enter long-term remission, mostly on a single antiepileptic drug. Combinations of 2 or at most 3 drugs are usually prescribed for those unresponsive to monotherapy. More than 30% of patients continue to have seizures despite pharmacological treatment.[1-5] For them, alternative managements such as a ketogenic diet, epilepsy surgery, or vagus nerve stimulation should be considered instead of serial addition of multiple drugs.[6,7] Nowadays, patients with seizure onset in recent years are seldom prescribed multiple drugs to manage the difficult-to-control seizures. But for those with seizures for many years, polytherapy with 3 or more drugs is not uncommon, especially when other strategies have been tried and failed or are not appropriate. Often, seizures are still not under control despite multiple antiepileptic drugs. These patients could be at risk for overtreatment, which does not bring efficacy but rather adverse effects.[8,9] In addition, both polytherapy and some certain antiepileptic drugs can aggravate seizures.[9-12]

Methods

Between October 2001 and October 2003, the histories were reviewed of all the patients in our clinic who had been given a diagnosis of epilepsy, who had taken antiepileptic drugs for more than 2 years, and who were free of active cerebral pathology such as encephalitis at acute stage, unresected brain tumor, acute brain hemorrhage, vascular lesion, or any deteriorating neurological presentation to indicate neurometabolic disorders. Those patients with persistent seizures who were using 3 or more drugs unchanged for at least 1 year were selected to undergo a drug readjustment. A written informed consent was obtained from all subjects and their guardians before study. We classified the patients into 3 groups according to seizure frequency: refractory (at least 1 significant seizure per month), free (no seizure for at least the previous year on unchanged treatment), and nonrefractory (seizures existent in the recent year). The following data

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were collected: age at enrollment, age of epilepsy onset, gender, neurodevelopment/mentality, and etiology. For patients with various ages, we used the Bayley Scales of Infant Development (second edition), the Wechsler Preschool and Primary Scale of Intelligence–Revised, or the Wechsler Intelligence Scale for Children (third edition) to evaluate neurodevelopmental status. The classifications of epilepsy type or epilepsy syndrome according to current guidelines of the International League Against Epilepsy,[13,14] antiepileptic drugs used and failed, alternative strategies tried other than antiepileptic drugs, present antiepileptic drugs, and previous responses to varied antiepileptic drugs of each patient were reevaluated. Ideally, we planned to reduce the number of antiepileptic drugs to 2 or at most 3, given in once- or twice-daily doses. The choices of medications to continue or introduce were based on some considerations: (1) drugs of choice for different seizure types or epileptic syndromes; (2) drugs to which patients experienced the best response and tolerability, if any; and (3) combined therapy with synergistic effects reported by the literature or with different mechanisms of action.[15-18] Some examples are valproate/lamotrigine, carbamazepine/topiramate, lamotrigine/topiramate, carbamazepine/valproate, and phenobarbital/topiramate. Older-generation sedative antiepileptic drugs were removed when possible. Antiepileptic drugs potentially aggravating seizures in certain seizure types were also selected for removal if this possibility were indicated after reevaluation. For example, we tried to remove phenytoin, carbamazepine, or vigabatrin from generalized seizures if possible. First, the antiepileptic drugs to remain were adjusted to a modest daily dose; then, those drugs to discontinue were tapered off gradually. Patients returned to the clinic on a monthly basis, and instructions were given. The path corresponded to the patient's response. After completion of the adjustment, patients were maintained on the same drugs for at least 1 year. After 1 year, we once again recorded the drugs used and the number as well as seizure frequency.

Statistical significance was evaluated by the χ^2 test, and $P \leq .05$ was considered significant.

Results

Thirty-one patients were identified. None were seizure free. Twenty-nine patients agreed to undergo the study. Basic data of gender, age at enrollment, age of seizure onset, seizure duration, etiology, and classification of seizure type or epilepsy syndrome are listed at Table 1. There were 14 boys and 15 girls. The mean ± standard deviation age of enrollment was 10.8 ± 5.7 years (range, 2 years 6 months to 24 years 3 months), and the age of seizure onset was 3.9 ± 3.6 years (range, 1 month to 10 years) with a seizure duration of 8.5 ± 4.7 years (range, 2-21 years). Seventeen patients (59%) were classified as having symptomatic epilepsy, 11 (38%) as having cryptogenic epilepsy, and only 1 (3%) as having idiopathic epilepsy. Twenty-seven (94%) patients had subnormal mentality, with severe mental retardation in 19 patients (66%), moderate mental retardation in 4 patients (14%), and mild mental retardation in 4 patients (14%). Ten patients had tried surgical intervention, vagus nerve stimulation, or ketogenic diet in addition to anticonvulsants. All patients had tried 3 or more drugs, with a mean number of 5.3 (range, 3-10 drugs). It took the patients a mean duration of 14.1 months (range, 6 months to 2 years) to complete the study. The number of antiepileptic drugs before and after the drug adjustment as well as the change of seizure frequency are shown in Tables 2 and 3. The patient who experienced worsening of seizures during the drug modification was lost from the study after 3 months. Eighteen patients (64.3%) had their drugs reduced, and the remaining 10 (35.7%) had a new drug introduced with removal of the others (rational polytherapy). Eleven patients experienced better seizure control, and 7 patients were unchanged in the formal group. Eight patients experienced seizure improvement, and 2 remained the same in the latter group. Carbamazepine was removed from 8 patients with generalized seizures, and 7 patients experienced better control of seizures, with 6 patients even becoming seizure free. Last, 4 patients were on monotherapy, 22 were on duotherapy, and 2 were taking triple drugs. The most common combined therapy was valproate/lamotrigine (n = 11) and carbamazepine/topiramate (n = 6; see Table 2). Among the seizure-free group (n = 11), 4 patients were on valproate/lamotrigine and 2 were on carbamazepine/topiramate. Case 11 had viral encephalitis, which resulted in refractory seizures and mental impairment. He developed status epilepticus during the study period. All oral medications were discontinued with intravenous phenobarbital loading. A ketogenic diet was tried during the hospitalization, and the patient gradually became seizure free.

From October 2001 to October 2004, a total of 183 children with epilepsy, excluding active cerebral pathology, treatable diseases, or deteriorating disorders, were regularly taking antiepileptic drugs and following up at our clinic for at least 1 year. The ratio of male to female patients was 1.5:1. The mean age (October 2004) was 9.2 ± 5.3 years, and the age of onset was 4.0 ± 3.7 years. Fifty-one patients (27.87%) were classified as idiopathic, 55 (30.05%) as cryptogenic, and 77 (42.08%) as symptomatic. In October 2004, we recorded the number of antiepileptic drugs being used and the status of seizure control. A total of 111 patients (60.66%) were on monotherapy, 68 (37.16%) were on duotherapy, and 4 (2.19%) were on triple drugs. Of the patients, 105 (57.38%) were seizure free, 27 (14.75%) were in refractory group, and the remaining 51 (27.87%) were in the nonrefractory group. In the seizure-free group, 86.7% was on monotherapy. On the contrary, 35.3% in the nonrefractroy group and 11.1% in the refractory group were using 1 drug (Figure 1). Most of the patients (64.7% in the nonrefractory group, 74.1% in the refractory group) who

Table 1. Clinical Characteristics of the 29 Patients

Case	Gender	Age	Age of Onset	Epilepsy Duration	Etiology	Seizure/Epilepsy
1	M	20 y 8 mo	10 y	10 y 8 mo	HSV encephalitis	Focal
2	F	16 y 1 mo	5 y	11 y 1 mo	HSV encephalitis	Focal
3	F	24 y 3 mo	3 y	21 y 3 mo	Prematurity with IVH	Generalized, atypical absence
4	F	12 y 2 mo	6 mo	11 y 8 mo	Tuberous sclerosis	Lennox-Gastaut syndrome
5	M	16 y	7 mo	15 y 5 mo	Cryptogenic	Unclassified
6	M	10 y 8 mo	10 mo	9 y 10 mo	Cryptogenic	Lennox-Gastaut syndrome
7	M	8 y 8 mo	2 y 3 mo	6 y 5 mo	Dandy-Walker variant	Atypical absence
8	M	8 y 5 mo	11 mo	7 y 6 mo	Cortical dysplasia	Focal
9	F	18 y 4 mo	10 y	8 y 4 mo	Heterotopia	Focal
10	M	10 y	2 y 1 mo	7 y 11 mo	Cryptogenic	Lennox-Gastaut syndrome
11	M	7 y 8 mo	5 y	2 y 8 mo	Viral encephalitis	Focal
12	M	8 y 6 mo	7 mo	7 y 11 mo	Hypoglycemic encephalopathy	Lennox-Gastaut syndrome
13	M	18 y 2 mo	5 mo	17 y 9 mo	Prematurity and perinatal asphyxia	Lennox-Gastaut syndrome
14	F	6 y 4 mo	4 mo	6 y	Perinatal asphyxia	Generalized
15	F	13 y 11 mo	5 y	8 y 11 mo	Cryptogenic	Unclassified
16	F	5 y 8 mo	1 mo	5 y 7 mo	Cryptogenic	Lennox-Gastaut syndrome
17	M	13 y 4 mo	3 y	10 y 4 mo	Tuberous sclerosis	Focal
18	F	15 y	6 mo	14 y 6 mo	Agenesis of corpus callosum	Focal
19	F	3 y	7 mo	2 y 5 mo	Lissencephaly	Lennox-Gastaut syndrome
20	F	2 y 6 mo	6 mo	2 y	Cryptogenic	Focal
21	M	11 y 9 mo	1 y	10 y 9 mo	Cryptogenic	Lennox-Gastaut syndrome
22	M	3 y 2 mo	3 mo	2 y 11 mo	Sturge-Weber syndrome	Focal
23	F	4 y 2 mo	5 mo	3 y 9 mo	Cryptogenic	Focal
24	F	11 y 10 mo	3 y	8 y 10 mo	Tuberous sclerosis	Focal
25	M	4 y 1 mo	9 mo	3 y 4 mo	Tuberous sclerosis	Lennox-Gastaut syndrome
26	F	10 y 9 mo	3 mo	10 y 6 mo	Cryptogenic	Focal
27	F	10 y 11 mo	7 mo	10 y 4 mo	Cryptogenic	Focal
28	F	3 y 4 mo	3 mo	3 y 1 mo	Cryptogenic	Focal
29	M	14 y 5 mo	10 y	4 y 5 mo	Idiopathic	Focal

NOTE: HSV = herpes simplex virus; IVH = intraventricular hemorrhage.

were not in the seizure-free group were using 2 antiepileptic drugs. There were 4 children who were on 3 drugs. Unfortunately, their seizure control was still not satisfactory. Seizure freedom was achieved in 84.3% (43 of 51) of patients who had idiopathic epilepsy, 41.8% (23 of 55) of those with cryptogenic epilepsy, and 50.6% (39 of 77) of those with symptomatic epilepsy (Figure 2). The seizure-free rate was statistically significantly higher in patients with idiopathic epilepsy than in those with a known or probable cerebral abnormality ($P < .005$). There was no significant difference between the cryptogenic and symptomatic groups ($P > .05$).

Discussion

It is not uncommon to find children who had difficult-to-control seizures for many years to be on multiple drugs. Often, patients and their parents were used to the situation even though there were no clinical benefits. Patients were usually mentally retarded, probably because of both the seizures per se and the adverse effects of the polytherapy. In this study, we tried to minimize and simplify the antiepileptic drugs (2 or 3 at most in the number of antiepileptic drugs, given as 1 or 2 divided daily doses). A total of 96.6% of the patients' seizure control did not worsen after the readjustment and reduction of the antiepileptic drugs. Instead, 65.5% got better, and 37.9% of the patients were seizure free. Although the results could possibly be attributed to the spontaneous remission of the seizures,[3,4] they still showed the fact that those patients were overtreated. One patient developed hand tremor, which we believed was a withdrawal symptom, but her parents recognized it as seizure aggravation. It happened in the beginning of our study, and this case gave us a very good lesson that clinicians should be very cautious, especially when a drug has been used for a long time. The seizure frequency in 9 patients (3 of whom had previous surgery and 6 of whom had previously tried a ketogenic diet) was unchanged, but the parents were glad that their children could take fewer drugs without seizure exacerbation. Two of the patients were undergoing presurgical evaluation when we wrote this article. We removed carbamazepine from patients with generalized epilepsy, including absence and myoclonic epilepses; introduced combined therapy with sodium valproate and lamotrigine; and 4 patients were seizure free. For partial epilepsy, we tried combined therapy with carbamazepine + topiramate in addition to sodium valproate + lamotrigine.[17] Two patients

Table 2. AEDs Tried, Nonpharmocological Strategies Tried, AEDs, and Seizure Frequency Before and After Drug Adjustment in 29 Patients

Case	No. of AEDs Tried	Other Strategies Tried	AEDs Before Study	Seizure Frequency* Before Study	Time to Complete	AEDs After Study	Seizure Frequency After Study
1	4	Callosotomy,VNS	CBZ, VGB, VPA	R	2 y	VPA, LTG	R (50%-75% reduction)
2	3	—	CBZ, VGB, VPA	R	1 y	CBZ, TPM	F
3	6	—	CBZ, AZM, LTG, VPA	R	1 y	VPA, LTG	N
4	5	Callosotomy, ketogenic diet	GBP, LTG, VGB	R	2 y	VPA, LTG	R (50% reduction)
5	4	—	CZP, CBZ, LTG	R	1 y	VPA, LTG	F
6	7	Callosotomy, ketogenic diet	CBZ, LTG, TPM, VPA	R	1 y	TPM, VPA	R (unchanged)
7	3	—	CBZ, CZP, LTG	R	8 mo	LTG, VPA	F
8	3	—	AZM, VGB, CBZ	N	8 mo	CBZ	F
9	3	—	CBZ, VPA, TPM	N	5 mo	CBZ, TPM	N (50%-75% reduction)
10	5	Callosotomy, ketogenic diet	CZP, CLB, VGB, VPA	R	1 y	VPA, LTG	R (unchanged)
11	4	—	CBZ, LTG, PB, TPM	R	10 mo	PB, ketogenic diet	F
12	4	—	CZP, VGB, VPA	R	1 y 6 mo	CZP, LTG, VPA	R (unchanged)
13	10	Callosotomy, ketogenic diet	CZP, LTG, VPA, VGB	R	2 y	LTG, VPA	R (unchanged)
14	4	Ketogenic diet	CBZ, CZP, VGB	N	9 mo	VGB	F
15	6	Callosotomy	CBZ, LTG, VPA	R	5 mo	LTG, VPA	F
16	5	Ketogenic diet	CZP, TPM, VGB	R	10 mo	VPA	R (unchanged)
17	6	—	CBZ, CZP, VGB	R	2 y	CBZ, TPM	N
18	5	Ketogenic diet	CBZ, LTG, TPM, VPA	R	8 mo	CBZ, TPM	R (unchanged)
19	5	Ketogenic diet	PB, TPM, VGB	R	2 y	PB, VPA	R (50% reduction
20	5	—	GBP, PB, TPM, VGB	R	2 y	GBP, TPM, VGB	R (unchanged)
21	6	Callosotomy	CBZ, LTG, TPM, VPA	R	8 mo	TPM, VPA	F
22	5	Hemispherectomy	PB, PHT, CZP, VGB	N	1 y 10 mo	PB, VGB	F
23	6	Ketogenic diet	CBZ, CZP, PB, TPM	R	1 y	PB, TPM	R (unchanged)
24	3	Ketogenic diet	CBZ, VGB, TPM	N	1 y	CBZ, TPM	F
25	7	—	CBZ, CZP, VGB, VPA	R	1 y	LTG, VPA	F
26	8	—	CZP, LTG, TPM, VGB, VPA	R	2 y	LTG, VPA	R (unchanged)
27	7	—	CBZ, CZP, TPM, VGB	R	10 mo	CBZ, TPM	N
28	7	—	PB, CZP, PHT, CLB, CBZ, VGB	N	3 mo	PB, TPM	New onset of SE
29	8	—	CZP, PB, VPA	R	10 mo	LTG, VPA	N

NOTE: AEDs = antiepileptic drugs; VNS = vagus nerve stimulation; CBZ = carbamazepine; VGB = vigabatrin; VPA = valproate; LTG = lamotrigine; TPM = topiramate; AZM = acetazolamide; GBP = gabapentin; CZP = clonazepam; PB = phenobarbital; PHT = phenytoin; CLB = clobazam; SE = status epilepticus.
*Patients were classified as refractory (R), nonrefractory (N), and seizure free (F) according to the status of seizure control in the past year.

were seizure free under carbamazepine + topiramate. One patient developed status epilepticus during the study period, and all oral medications were discontinued with phenobarbital loading. During the hospitalization, a ketogenic diet was also tried, and the patient gradually became seizure free. Polytherapy and some certain drugs do aggravate seizures, and this may be why our patients had a beneficial effect from drug reduction. Choosing an appropriate antiepileptic drug for the seizure type or syndrome is very important when initiating pharmacotherapy. When monotherapy failed to control the seizures, combined therapy with 2 or at most 3 drugs may be indicated. Evidence is emerging that certain combinations offer better efficacy than others do (synergism).[15] A few patients become seizure free on 3 antiepileptic drugs, but treatment with 4 or more drugs is not likely to be successful. In our patients,

Table 3. Comparison of the Number of AEDs and Seizure Control Before and After Drug Adjustment

	Before	After
Mean number of AEDs	3.6	1.9
Seizure frequency	R: 23 N: 6	F: 11 N: 5 R: 12
Summary of change of seizure control		Improved (N: 19, 65.5%) R → F: 7 R → N: 4 R → R: 3 N → F: 4 N → N: 1 Unchanged (N: 9, 31.0%) Worse (N: 1, 3.4%)

NOTE: AEDs = antiepileptic drugs; R = refractory; N = nonrefractory; F = seizure free.

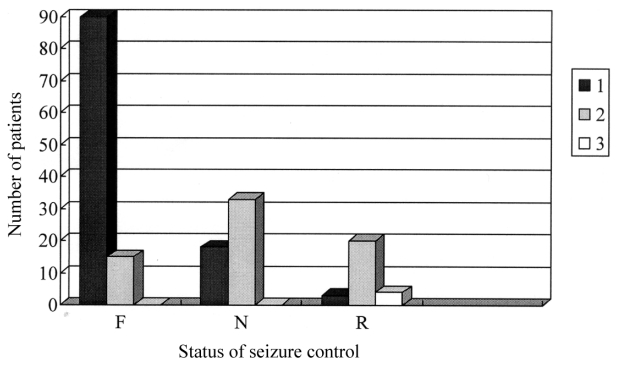

Figure 1. The number of patients with monotherapy (1), duotherapy (2), or triple drugs (3) in 3 different groups: seizure-free (F), nonrefractory (N), and refractory (R).

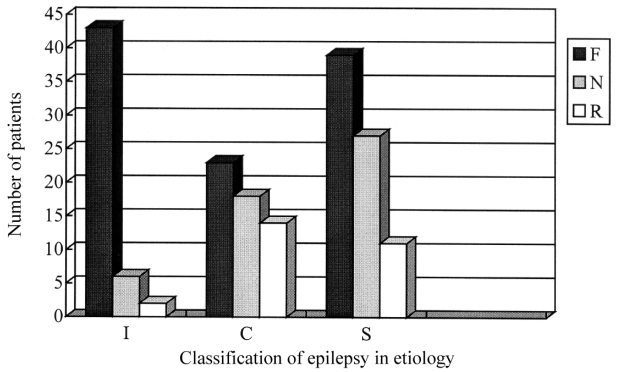

Figure 2. The number of patients who were seizure free (F), nonrefractory (N), or refractory (R) in each group of idiopathic (I), cryptogenic (C), or symptomatic (S) epilepsy.

none used more than 3 antiepileptic drugs. Only 4 patients were taking 3 drugs, and, unfortunately, seizures were still poorly controlled.

Defined or probable remote symptomatic etiology of seizures is significantly associated with long-term refractoriness, as indicated by our cases. Patients with high initial seizure frequency, lack of a response to initial treatment with antiepileptic drugs, occurrence of status epilepticus, changes in type of epilepsy during the clinical course, and so on are also likely to have refractory epilepsy.[19-21] It seems that patients with epilepsy comprise 2 distinct populations: easy to control and difficult to control in terms of seizure control from the outset. For patients with difficult-to-control seizures, it is reasonable to try every effort to find the right drug or drugs for seizure freedom. However, serial addition of multiple antiepileptic drugs has little opportunity to achieve that goal. Alternative strategies might be considered early in the appropriate timing. It is a long way to go. For those patients and their families who are facing the tough periods, it may be of uttermost importance to accompany and support them to conquer the obstacles together.

References

1. Brodie MJ, Kwan P. Staged approach to epilepsy management. *Neurology*. 2002;58(suppl 5):S2-S8.
2. Sillanpaa M. Remission of seizures and predictors of intractability in long-term follow-up. *Epilepsia*. 1993;34:930-936.
3. Sillanpaa M, Jalava M, Kaleva O, Shinnar S. Long-term prognosis of seizures with onset in childhood. *N Engl J Med*. 1998; 338:1715-1722.
4. Aso K, Watanabe K. Limitations in the medical treatment of cryptogenic or symptomatic localization-related epilepsies of childhood onset. *Epilepsia*. 2000;41(suppl 9):18-20.
5. Ohtsuka Y, Yoshinaga H, Kobayashi K, et al. Predictors and underlying causes of medically intractable localization-related epilepsy in childhood. *Pediatr Neurol*. 2001;24:209-213.
6. Gilman JT, Duchowny M, Jayakar P, Resnick TJ. Medical intractability in children evaluated for epilepsy surgery. *Neurology*. 1994;44:1341-1343.
7. Benbadis SR, Tatum WO, Vale FL. When drugs don't work: an algorithmic approach to medically intractable epilepsy. *Neurology*. 2000;55:1780-1784.
8. Bourgeois BF. Reducing overtreatment. *Epilepsy Res*. 2002;52: 53-60.
9. Holmes GL. Overtreatment in children with epilepsy. *Epilepsy Res*. 2002;52:35-42.
10. Genton P, McMenamin J. Summary. Aggravation of seizures by antiepileptic drugs: what to do in clinical practice. *Epilepsia*. 1998;39(suppl 3):S26-S29.
11. Guerrini R, Belmonte A, Genton P. Antiepileptic drug-induced worsening of seizures in children. *Epilepsia*. 1998;39(suppl 3): S2-S10.
12. Bourgeois BF. Chronic management of seizures in the syndromes of idiopathic generalized epilepsy. *Epilepsia*. 2003;44(suppl 2): 27-32.
13. Commission on Classification and Terminology of the International League Against Epilepsy. Proposal for revised classification of epilepsies and epileptic syndromes. *Epilepsia*. 1989;30:389-399.
14. Commission on Classification and Terminology of the International League Against Epilepsy. Proposal for revised clinical and electroencephalographic classification of epileptic seizures. *Epilepsia*. 1981;22:489-501.
15. Deckers CL, Czuczwar SJ, Hekster YA, et al. Selection of antiepileptic drug polytherapy based on mechanisms of action: the evidence reviewed. *Epilepsia*. 2000;41:1364-1374.
16. Brodie MJ. Management strategies for refractory localization-related seizures. *Epilepsia*. 2001;42(suppl 3):27-30.
17. Pisani F, Oteri G, Russo MF, et al. The efficacy of valproate-lamotrigine comedication in refractory complex partial seizures: evidence for a pharmacodynamic interaction. *Epilepsia*. 1999;40: 1141-1146.
18. Stephen LJ, Sills GJ, Brodie MJ. Lamotrigine and topiramate may be a useful combination. *Lancet*. 1998;351:958-959.

19. Prognosis of epilepsy in newly referred patients: a multicenter prospective study of the effects of monotherapy on the long-term course of epilepsy. Collaborative Group for the Study of Epilepsy. *Epilepsia*. 1992;33:45-51.
20. Kwan P, Brodie MJ. Early identification of refractory epilepsy. *N Engl J Med*. 2000;342:314-319.
22. Ohtsuka Y, Yoshinaga H, Kobayashi K. Refractory childhood epilepsy and factors related to refractoriness. *Epilepsia*. 2000; 41(suppl 9):14-17.