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Seizure control with antiepileptic drug therapy in 517 consecutive adult outpatients at the Kork Epilepsy Centre

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ABSTRACT – In order to assess the efficacy of modern antiepileptic drug (AED) therapy, we collected data from 517 consecutive adult outpatients referred to our centre between March and August 2011. In total, 211 patients (40.8%) were treated with monotherapy, 208 patients (40.2%) with a combination of two AEDs, and for the remaining patients (*n*=98; 19%) more than two AEDs were combined. The most common AEDs were valproate, lamotrigine, carbamazepine, and levetiracetam. Of the recent AEDs, levetiracetam was the leading drug with regards to drug combinations. Freedom of seizures for more than one year was achieved in 291 patients (56.3%). Under monotherapy, 168 patients (32.5% of all patients; 79.6% of patients with monotherapy) became seizure-free. Seizure-freedom with two AEDs was achieved in 103 patients (19.9% of all patients; 49.5% of patients with two AEDs) and in 20 patients with three AEDs (3.9% of all patients; 25.3% of patients with three AEDs). We conclude from this cross-sectional survey in a large patient group that combinations may still lead to treatment success in a considerable proportion of patients.

Key words: epilepsy, antiepileptic drug, adult, seizure control, monotherapy, drug combination

Many new antiepileptic drugs (AEDs) have been introduced to treat epilepsy since the launch of vigabatrin. However, it remains questionable whether they are effective in markedly reducing the number of drug-resistant epilepsy patients or improving the quality of life in a considerable proportion of hitherto difficult-to-treat patients. The latter is mainly influenced by additional factors such as co-existing depression or AED-related adverse events rather than by seizure frequency itself (Gilliam, 2002). Due to the pharmacological profile of some of the new AEDs and their comparable efficacy, it has been claimed that the use of these new AEDs may considerably improve the individual quality of life in epilepsy patients even if they are

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drug-resistant (Diener *et al.*, 2008). According to the Guidelines of the German Neurological Society (Diener *et al.*, 2008), the major rationale for using some of the new AEDs, both as primary and subsequent therapy and either monotherapy or combination, is the lack of interactions and potential long-term side effects due to enzyme induction, since efficacy has been shown to be comparable or non-inferior to classical AEDs, such as phenytoin, carbamazepine or valproic acid, at least in monotherapy trials in newly diagnosed adult patients with focal seizures (Dam *et al.*, 1989; Brodie *et al.*, 1995; Reunanen *et al.*, 1996; Christe *et al.*, 1997; Guerreiro *et al.*, 1997; Chadwick *et al.*, 1998; Brodie *et al.*, 1999; Steiner *et al.*, 1999; Privitera *et al.*, 2003; Steinhoff *et al.*, 2005; Brodie *et al.*, 2007). The dogma of monotherapy as the golden standard of AED therapy (Shorvon and Reynolds, 1977; Reynolds and Shorvon, 1981) has not really been questioned. Studies that addressed the effectiveness of add-on treatment versus alternative monotherapy after the failure of first monotherapy did not reveal unequivocal results (Kwan and Brodie, 2000a; Beghi *et al.*, 2003). Monotherapy is plausibly superior (Shorvon and Reynolds, 1977; Reynolds and Shorvon, 1981; Diener *et al.*, 2008), but this has not been convincingly shown (Deckers *et al.*, 2001). Moreover, more recent studies that included new AEDs suggest that seizure freedom may sometimes still be achieved by means of add-on treatment even in hitherto drug-resistant epilepsies (Callaghan *et al.*, 2007; Luciano and Shorvon, 2007), although the improvement in efficacy has been rated as somewhat disappointing (Beyenburg *et al.*, 2010; Beyenburg *et al.*, 2012; Stephen *et al.*, 2012).

From a practical point of view, it is interesting to determine whether this uncertainty affects the choice for a second, third or later additional AED in patients who are still not seizure-free or develop intolerable side effects, but also whether newly re-developed ideas such as rational drug therapy (French and Faught, 2009) have an impact on real life. This therefore leads to the hypothesis that combinations of at least some AEDs with different modes of action may be more efficacious and better tolerable than, for example, the combination of two sodium channel blocking agents (French and Faught, 2009; Sake *et al.*, 2010).

At the Kork Epilepsy Centre, it is a well-established tradition that the most experienced staff members regularly see all outpatients referred to this tertiary epilepsy centre. Combining both youngsters and adults, around 6,000 outpatients are seen per year. Many of them have been treated by the same person over years or sometimes decades which makes it somewhat difficult to offer the necessary appointments for newly referred patients. However, it offers a unique possibility to assess the outcome of therapy for a very homogenous group with a chronic disease.

In this study, we investigated consecutive adult outpatients seen and treated exclusively by one of the authors (BJS) in order to investigate: i) the proportion of patients with seizure freedom for more than a year or a seizure-free period three times that of the previous longest seizure-free interval, in line with the recent definition of unequivocal effects of treatment in drug-resistant epilepsy (Kwan *et al.*, 2010) (referred to as "seizure-free"); ii) the distribution of monotherapies and combinations, and the therapeutic effect of these strategies; iii) the proportion of patients who only became seizure-free with combinations; iv) the most common AEDs both in monotherapy and combination; and finally v) the rationale behind the preferred monotherapies and combinations.

Patients and methods

We consecutively collected data of all adult outpatients seen and treated by one of the authors (BJS) between March 1st and August 31st, 2011. These patients were regularly referred by general practitioners or neurologists in private practice. We included only those patients who had been seen by us before, with a minimum period of personal observation and treatment of 12 months and at least one prior referral. Patients who had undergone epilepsy surgery (n=29), were without AED medication (n=11), or had additional non-epileptic psychogenic seizures (n=14), were excluded. Further inclusion or exclusion criteria were not applied. Under these circumstances, 517 patients were included. In each case, demographic data, seizures and epilepsy classification, AED regimen, dosage, seizure frequency, and adverse effects were documented. In the case of seizure freedom of more than a year, an assessment was made to address whether any reduction or discontinuation of AEDs, due to longer seizure-free intervals, had been attempted and whether this was successful.

Statistical analysis

Mean values, standard deviation, and standard error to the mean were calculated for the parametric variables. The total number and percentages were calculated for categorical variables. One-way analysis of variance (ANOVA) was performed with Statistica (Statsoft ®, version 8.0). The four groups of medication, levetiracetam (LEV), carbamazepine (CBZ), LEV as add-on to another AED, and CBZ added to another AED, served as categorical predictors. The dependant variable was seizure-free years. Post-hoc analysis was performed using the Newman-Keuls test. Statistical significance was determined at $p<0.05$.

Results

We recruited 517 consecutive adult patients (mean age: 41.6 years; range: 16-89 years). Of these, 269 patients (52%) were female and 248 (48%) male. Mean age at onset of epilepsy was 15.2 years (range: 0-84 years), mean duration of epilepsy 26.4 years (range: 2-68 years), and the mean duration of follow-up at our centre 14.7 years (range: 1-45 years). Epilepsy syndromes were classified according to the new ILAE proposal (Berg *et al*., 2010).

Patients included 235 (45.5%) with structural/metabolic epilepsies, 104 (20.1%) with genetic epilepsies, and 178 (34.4%) with epilepsies of unknown aetiology. Further consideration for specific epilepsy syndromes revealed eight patients with juvenile absence epilepsy, 16 patients with juvenile myoclonic epilepsy, three patients with Lennox-Gastaut syndrome, and two patients with Dravet syndrome.

Seizure freedom was achieved in 291 patients (56.3%). Of these, 168 (32.5%) were treated by monotherapy, 103 (19.9%) with two AEDs, and 20 (3.9%) with three AEDs. No patient became seizure-free with more than three AEDs in combination.

Of 517 patients, 211 received monotherapy (40.8%). The demographic and clinical variables are displayed in *table 1*. The most commonly prescribed drug was valproic acid (VPA), followed by lamotrigine (LTG), CBZ, and LEV. Apparently, VPA was almost exclusively used for genetic epilepsies whereas CBZ and oxcarbazepine (OXC) were applied almost only for structural/metabolic or aetiologically-unresolved epilepsy syndromes. Although LEV is not labelled for monotherapy of genetic epilepsies in Germany, these syndromes were treated using LEV monotherapy, corresponding to a fifth of all patients with LEV monotherapy. In total, 168 patients (32.5% of all patients; 79.6% of patients with monotherapy) became seizure-free. The percentage of seizure-free patients ranged from 57.1% for OXC to 100% for PRM. The distribution between genetic and other epilepsy syndromes is also shown in *table 1*. Not displayed in the table are 4 seizure-free patients treated with bromides (*n*=2) and sulthiame (*n*=2) and 2 patients with persistent seizures who were treated with eslicarbazepine acetate (ESL) and ethosuximide (ESM), respectively.

In total, 208 patients were treated with a combination of two AEDs. The most commonly prescribed combinations are presented in *table 2* and comprised: LTG+LEV (*n*=25; 12.0%), OXC+LEV (*n*=19; 9.0%), VPA+LTG (*n*=15; 7.1%), and VPA+LEV (*n*=14; 6.6%). The AEDs most commonly used for combination therapy consisting of two drugs were as follows (in order): LEV (*n*=75; 36.1%), LTG (*n*=72; 34.1%), OXC (*n*=48; 22.7%), VPA (*n*=46; 21.8%), and CBZ (*n*=31; 14.7%). Again, CBZ and OXC were exclusively applied to structural/metabolic or aetiologically-unknown epilepsy syndromes, VPA to genetic epilepsies, and LTG and LEV independently of the underlying aetiology. Seizure freedom with two AEDs was achieved in 103 patients (19.9% of all patients; 49.5% of all patients with two AEDs). The most successful seizure outcome was achieved with CBZ+PHT (66.6%) and the lowest rate was found for OXC+LTG (16.7%).

Table 1. Demographic and clinical patient variables for monotherapy.

Variables	CBZ *n*=37	LEV *n*=27	LTG *n*=46	OXC *n*=14	PB *n*=8	PHT *n*=13	PRM *n*=7	TPM *n*=5	VPA *n*=48
Male (%)	60.5	53.5	29.8	42.9	25	57.1	42.9	40	56
Female (%)	39.5	46.5	70.2	57.1	75	42.9	57.1	60	44
Age (years)	47	50	35	36	49	54	55	50	39
SD; SEM	15.5; 2.5	16.6; 2.7	15.4; 2.3	11.6; 3.1	10.1; 3.6	16.1; 4.3	5.6; 2.1	17.2; 7.7	16.6; 2.3
Epilepsy type (%)									
Genetic	2.6	21.4	25.5	0	37.5	7.1	42.8	20	92.1
Others	97.4	78.6	74.5	100	62.5	92.9	57.1	80	7.9
Seizure outcome (%)									
Seizure-free	89.2	81.5	63.5	57.1	87.5	76.9	100	80	92.1
Persistant	10.8	18.5	36.5	42.9	12.5	23.1	0	20	7.9
Daily dose (mg)	830	1,375	325	1,510	159	270	554	200	1,095
SD; SEM	417; 67	753; 142	152; 22	472; 126	68; 24	89; 24	269; 102	178; 79	447; 63
range	300-1,800	500-4,000	100-700	900-2,400	50-250	100-400	250-1,000	50-500	450-2,500

n: number of patients; SD: standard deviation; SEM: standard error of mean; CBZ: carbamazepine; LEV: levetiracetam; LTG: lamotrigine; OXC: oxcarbazepine; PB: phenobarbital; PHT: phenytoin; PRM: primidone; TPM: topiramate; VPA: valproate.

Table 2. Demographic and clinical variables for the combination of two antiepileptic drugs.

Variables	CBZ+PHT *n*=6	CBZ+LEV *n*=13	LTG+LEV *n*=25	LTG+TPM *n*=6	OXC+LTG *n*=12	OXC+LEV *n*=19	VPA+LEV *n*=14	VPA+LTG *n*=15	Others *n*=98
Male (%)	50	31	44	16.7	50	57.8	42.9	60	46
Female (%)	50	69	56	83.3	50	42.1	57.1	40	54
Age (years)	47	42	39	42	36	36	39	32	41
SD; SEM	10.2; 2.2	17; 4.7	14.7; 2.9	23.1; 9.2	14.4; 4.2	12.9; 3	12.1; 3.2	12.5; 3.2	16.7; 1.7
Epilepsy type (%)									
Genetic	0	0	13.2	20	0	0	71.4	13.3	14.2
Others	100	100	86.8	80	100	100	28.5	86.6	85.7
Probability of seizure outcome									
Seizure-free (%)	66.6	46.2	28	50	16.7	31.6	57.1	40	38.8
Persistant (%)	33.3	53.8	72	50	83.3	68.4	42.9	60	61.2
Daily dose 1 (mg)	917	1,250	440	300	1,720	1,892	1,471	1,147	N/A
SD; SEM	491; 201	475; 132	156; 31	122; 50	854; 246	644; 148	609; 163	659; 177	
Range	600-1,800	200-2,100	100-700	100-400	400-3,900	600-2,700	500-2,500	250-2,400	
Daily dose 2 (mg)	225	1823	2280	175	579	1896	1643	278	N/A
SD; SEM	82; 24	1064; 295	902; 180	82; 33	241; 69	1151; 264	745; 199	133; 34	
Range	150-350	200-4,000	1,000-4,000	50-250	300-1,000	200-4,000	1,000-3,000	100-600	

n: number of patients; SD: standard deviation; SEM: standard error of mean; CBZ: carbamazepine; LEV: levetiracetam; LTG: lamotrigine; OXC: oxcarbazepine; PHT: phenytoin; TPM: topiramate; VPA: valproate.

Among the 103 seizure-free patients with a combination of two AEDs, the most commonly used drugs were CBZ and LEV. In 27 cases, the discontinuation of one drug had been attempted but this was unsuccessful due to seizure relapse; in these patients, the combination was re-established with sustained seizure freedom. In the other cases, discontinuation of one of the concomitant AEDs had either not been considered or was not yet started.

For a combination of two AEDs, CBZ was mostly combined with LEV (*n*=13) or PHT (*n*=6). The leading combination of drugs with LEV included LTG (*n*=25), followed by OXC (*n*=19), VPA (*n*=14), CBZ (*n*=13), and others. The clinical and demographic characteristics of the seizure-free cases are presented in *table 3*.

The result of the ANOVA test for the treatment *versus* seizure-free years was highly significant ($F[3.88]=38.680$, $p<0.001$). Patients taking CBZ were seizure-free for significantly longer, relative to the LEV group; illustrated in *figure 1*. *Table 4* shows the ANOVA decomposition using the Newman-Keuls *post-hoc* test.

Seventy-nine patients received a combination of three AEDs, of whom 20 had been seizure-free for more than one year (3.9% of all patients; 25.3% of patients with more than two AEDs). VPA was the most constantly prescribed substance in this group (*n*=25), followed by PB (*n*=12), OXC (*n*=11), and CBZ (*n*=10). Only 13 patients (2.5%) were treated with four drugs and all of them had persistent seizures.

Considering the mode of action of AEDs, we analysed the results according to the main mechanism of action. PHT, CBZ, OXC, ESL, and LTG were classified as sodium channel blockers in line with previous studies (Sake *et al*., 2010; Villanueva *et al*., 2012). When we investigated the efficacy of combinations, we observed that the distribution of patients who were treated with combinations containing at least one sodium channel blocker versus patients without sodium channel blockers was not evenly distributed. Nevertheless, this data was analysed and the rates of seizure freedom in these two groups are presented in *table 5*, demonstrating that no clear difference was apparent.

At the time of this survey, the most recent AEDs were ESL and lacosamide (LCM). Both were used in our patient series but were not used often enough to be part of the larger groups mentioned above. Retigabine (RTG) was launched in Germany in the summer of 2011 and only one patient in the series was taking RTG as add-on treatment; the patient was treated during an open extension as part of an RTG trial. ESL and LCM were mainly given in combination with one or two other drugs. There was one case of off-label monotherapy with ESL. ESL was given in 13 cases (6.2%).

Table 3. Clinical and demographic characteristics for seizure-free patients taking CBZ and LEV.

Variables	CBZ *n*=34	LEV *n*=22	CBZ add-on with one other AED *n*=12	LEV add-on with one other AED *n*=24
Male (%)	61.8	59.1	41.7	37.5
Female (%)	38.2	40.9	59.3	62.5
Age (years)	48	49	47	39
SD; SEM	14.9; 2.6	16.9; 3.6	13.1; 3.8	12.4; 2.5
Seizure-free (years)	8 (2.5; 0.4)	3 (1.5; 0.3)	8 (2.4; 0.7)	3 (2.4; 0.5)
Epilepsy type (%)				
Genetic	2.3	27.3	0	41.7
Others	97.7	72.7	100	58.3
Daily dose (mg)	782	1,455	1,127	1,417
SD; SEM	394; 68	815; 174	336; 54	804; 162
range	300-1,800	500-4,000	600-1,650	1,000-3,000

n: number of patients; SD: standard deviation; SEM: standard error of mean; CBZ: carbamazepine; LEV: levetiracetam.

One patient was seizure-free (7.6%) under the combination of ESL with LEV. LCM was given to 25 patients (11.8%). One patient was seizure-free (4.5%) under the combination of LCM with LEV and OXC.

Discussion

This study shows that among outpatients referred to a tertiary epilepsy centre, AED therapy is associated with a satisfactory and sustained seizure-free situation for a considerable percentage. We included only patients who had been treated by us for longer than one year and attended at least one previous appointment in order to collect only cases in which the course of the treatment could be adequately assessed. As many as 291 patients (56.3%) were seizure-free for more than one year. Seizure freedom was achieved with combination in 123 (23.8%) cases (103 patients with two AEDs and 20 patients with three AEDs). These figures are very similar to those of the survey in a large Scottish patient group where 20.4% of patients were seizure-free with combinations, of which the majority were treated with two AEDs, however, patients were still seizure-free with three (17.5% seizure-free patients) and even four AEDs (1.2% seizure-free) (Stephen *et al*., 2012).

The patients assessed in this survey could be divided into two major groups with one group reflecting patients who had become seizure-free several years or even sometimes decades ago, but who still remained on their original AED regimen. It is not surprising that many of these patients were still on AEDs such as CBZ, VPA or even PHT and barbiturates, in spite of the potential and sometimes clinically relevant drawbacks concerning long-term tolerability and interactions with other AEDs, as well as any co-medication drugs (Relling *et al*., 2000; Sheth and Harden, 2007; Diener *et al*., 2008; Beyenburg *et al*., 2012). One should not forget that the burden of enzyme induction does not necessarily lead to long-term side effects in every patient and that there is a disadvantage associated with some of the new AEDs which may interact by enzyme induction or, in addition, other mechanisms (Staack *et al*., 2007). It is certainly not surprising that seizure-free patients on CBZ remained on this AED for significantly longer than patients who had become seizure-free with LEV (*figure 1 and table 4*). However, our statistical approach underlines the enormous importance of AED choice early in the course of the

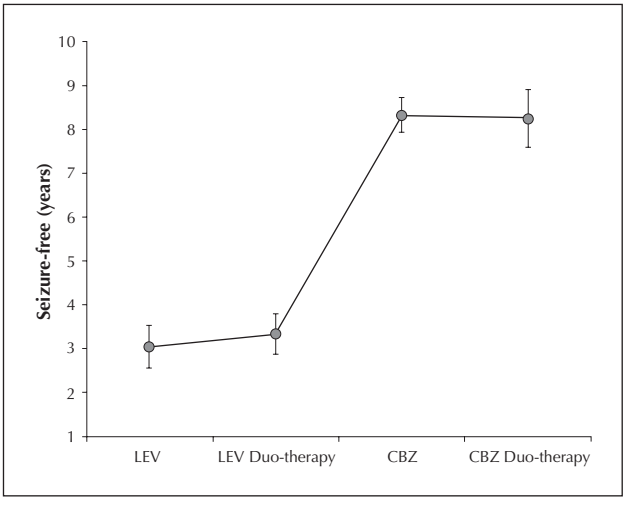

Figure 1. Seizure-free years with carbamazepine *versus* levetiracetam (as monotherapy and combination with another AED).

Table 4. Results of Newman-Keuls post-hoc test. ANOVA, with CBZ and LEV as categorical predictors and seizure-free years as the dependent variable, shows statistically significant differences for the duration of seizure freedom.

	LEV	CBZ	CBZ Add-on	LEV Add-on
LEV		**0.000145**	**0.000107**	0.690218
CBZ	**0.000145**		0.918938	**0.000107**
CBZ-Add-on	**0.000107**	0.918938		**0.000113**
LEV-Add-on	0.690218	**0.000107**	**0.000113**	

CBZ: carbamazepine; LEV: levetiracetam; $p<0.05$ (in bold) is statistically significant.

disease. Providing good tolerability, a high percentage of patients will become seizure-free with the first AED (Kwan and Brodie, 2000b). Therefore, even in the case of long-term side effects that are more probable with enzyme-inducing AEDs, such as CBZ, adult patients will probably remain on their initial drug to avoid any risk of seizure relapse. This is clearly supported by our data and should remind neurologists of their major responsibility in the management of treatment at this stage of therapy.

The mean dosage of CBZ in seizure-free patients was 782 mg and slightly higher dosages have been reported as the recommended first maintenance dosage in newly diagnosed adult patients who were treated with immediate-release (Reunanen *et al*., 1996) or controlled-release CBZ (Brodie *et al*., 2007). All of our patients were treated with a controlled-release formulation since the pharmacological advantages of such a formulation are obvious and well described (Ficker *et al*., 2005). The possible, slightly lower bioavailability of slow-release CBZ formulations (Larkin *et al*., 1989) was probably not the main reason for the relatively high dosages. Even the latest guidelines of the German Neurological Society (Diener *et al*., 2008) recommend a first maintenance dosage of 600 mg, thus it is not surprising that the mean dosage in our patients was ultimately slightly higher. Most patients had been treated with CBZ for a longer period of time and a slightly higher and more efficacious dosage was a reflection of the pragmatic and traditional attitude of our centre.

If seizure freedom is achieved, the quality of life of epilepsy patients is similar to that of healthy people (Birbeck *et al*., 2002). This underlines the importance for reliable seizure freedom and explains why many seizure-free patients choose not to subject themselves to any risk that may increase the possibility of seizure relapse. These factors are probably the main cause for commonly unaltered AED therapy and may even explain the attitude of some patients who accept even long-term side effects rather than agreeing to AED reduction or change. Our data reflect that the efficacy of adjunctive enzyme-inducing AEDs, relative to non-enzyme-inducing AEDs, is not necessarily worse, as has been reported recently in an extensive meta-analysis (Beyenburg *et al*., 2012). The main issue is therefore the long-term tolerability that may be potentially more impaired under enzyme-inducing drugs (Diener *et al*., 2008; Beyenburg *et al*., 2012) which was probably the driving force in the second patient group of our study. This group comprised patients whose

Table 5. Efficacy of combinations with and without sodium channel blockers (phenytoin, carbamazepine, oxcarbazepine, eslicarbazepine actetate and lamotrigine).

	No. of patients	No. of seizure-free patients
Combination of two antiepileptic drugs		
Total	208	103 (49.5%)
with sodium channel blocker	159 (76%)	80 (53%)
without sodium channel blocker	49 (24%)	23 (47%)
Combination of three antiepileptic drugs		
Total	79	20 (25.3%)
with sodium channel blocker	64 (81%)	16 (25%)
without sodium channel blocker	15 (19%)	4 (27%)
Combination of four antiepileptic drugs		None

AED strategy was changed more recently before they became seizure-free. Among the seizure-free patients, the major AEDs used were CBZ and VPA in Group 1 and LTG and LEV in Group 2. Thus, there was an apparent move to the more recent AEDs which was proposed, at least for monotherapy, in the guidelines of the German Neurological Society (Diener *et al*., 2008). However, in accordance with many other reports, we could not find a difference in efficacy between first and second generation *versus* new AEDs.

Following the introduction of a variety of new AEDs with different modes of action and pharmacological profiles, it remains questionable as to whether these AEDs have had an effect on markedly reducing the percentage of patients with previous drug-resistant epilepsies (Beyenburg *et al*., 2010). The rather discouraging data by Kwan and Brodie (Kwan and Brodie, 2000b) of newly diagnosed adult patients have been questioned more recently. Both Luciano and Shorvon and Callaghan *et al*. (2007) reported that even in hitherto AED-resistant patients, a considerable percentage still benefited from the introduction of new AEDs, either as alternative or add-on treatment. One reason for these more encouraging data on efficacy may have been due to the fact that new AEDs, such as LEV, were often reported in drug-resistant patients; LEV was given to 101 of 125 patients in the study of Luciano and Shorvon (2007) and was introduced to 12% of patients in the study of Callaghan *et al*. (2007). However, this is clearly not the only reason for the better efficacy of LEV reported in these two crucial trials. The improved practicability, efficacy, and tolerability profile of LEV is a major achievement in epilepsy therapy over the last two decades, both as monotherapy and add-on treatment. This was clearly reflected by our data showing that a majority of patients who became seizure-free with add-on regimens were taking LEV.

Compared to the reports of drug-resistant epilepsy patients who finally became seizure-free with an alternative AED strategy (Callaghan *et al*., 2007; Luciano and Shorvon, 2007), the rate of seizure-free patients was much higher in our survey, indicating clearly that many of our patients were easier to treat. Even if we excluded patients with classical idiopathic generalised epilepsy syndromes, the remaining patients, who should have a poor prognosis, had a better outcome than those patients with drug-resistant epilepsies. It has been shown that significantly better seizure outcome may be achieved if patients are referred from general neurologists to specialised epileptologists (Szaflarski *et al*., 2008) which may have also influenced the seizure outcome results presented in this study. One might suggest that the selection of patients may have been influenced by a bias, since unsatisfied patients may have been overlooked by not returning to the study.

Most patients were seizure-free with monotherapy. The interesting and somewhat surprising message of our paper is that 123 patients (23.8% of the total 517 patients) required a second (*n*=103; 9.9%) or even third drug (*n*=20; 3.9%) to become seizure-free. This does not necessarily exclude that these patients would have remained seizure-free with monotherapy with the second or third drug, because many seizure-free patients would have refused any further treatment once they had become seizure-free. However, it remains a fact that, for these patients, add-on treatment was essential to ultimately become seizure-free. This also indicates that the failure of initial monotherapy or even other drug strategies does not necessarily mean that patients may not become seizure-free. In this study, for 27 patients who had become seizure-free with combinations, the attempt to reduce the previous AED was abandoned due to seizure relapse (22% of all patients who were seizure-free with combinations of AEDs). Thus, for at least these patients, treatment combination as the best effective strategy was justified. Although we were aware of a handful of patients who were seizure-free and took more than three AEDs, these cases were not included during our cross-sectional survey from March to August 2011, since it was evident that a combination of more than three AEDs was not normally effective. In the large patient group recently reported by Stephen *et al*. (2012), 1.2% of patients were seizure-free with four AEDs. Similar to our study, the majority of patients were treated with two AEDs.

With regards to LEV as the preferred add-on drug in seizure-free patients, one may speculate whether its additional and potentially complimentary mode of action may have contributed to its effect beyond its almost perfect pharmacological profile as an add-on therapy. LEV add-on treatment is therefore a rational approach for polytherapy providing a different mechanism of action. The mode of action of LEV is unique and relies on the selective binding at the SV2A binding site (Bialer *et al*., 2010). Our data do not allow us to draw any conclusions with regards to the mode of action. *Table 5* shows clearly that the probability of seizure control was apparently not influenced by the underlying mode of action of the AEDs combined, at least when combinations with or without sodium-blocking agents were compared. Moreover, the highest rate of seizure freedom was achieved with the classical combination of CBZ and PHT. The small sample size of the groups does not allow us to draw any conclusions with regards to better or less effective AED combinations. However, the concept of rational polytherapy that has emerged in conjunction with new AEDs with novel modes of action (Sake *et al*., 2010) is certainly fascinating and is worth following in the future. Possible drug combinations of drugs with different modes of

actions, such as LCM or RTG that were barely used in this data set, in the future may lead to more convincing rationales. At present, the best guideline for rational polytherapy is the avoidance of pharmacodynamic and pharmacokinetic side effects (French and Faught, 2009).

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