Original article

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Early add-on treatment *vs* alternative monotherapy in patients with partial epilepsy

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ABSTRACT – *Aim*. The aim of this study was to evaluate the impact of two different therapeutic strategies in patients with partial seizures who were intractable to the first prescribed antiepileptic drug (AED); alternative monotherapy vs early add-on treatment.

Methods. We conducted an open, cluster-randomised, prospective, controlled trial in patients with persistent partial seizures, despite treatment with one AED, who were never administered any other AEDs. Neurologists were randomised to two strategies: in group A, an alternative monotherapy with a second AED was employed; in group B, add-on treatment with a second AED was employed. The primary outcome was the percentage of seizure-free patients during a two-month period after six months of treatment. The secondary outcomes were: (i) the percentage of patients achieving a 50% reduction in the number of seizures at six months; (ii) the quality of life based on the Quality Of Life In Epilepsy scale; and (iii) tolerability.

Results. A total of 143 neurologists were included and randomised, and 264 patients were evaluated. At six months, the primary outcome was 51% in group A and 45% in group B (p=0.34). The percentage of patients achieving a 50% reduction in the number of seizures at six months was 76% in group A and 84% in group B (p=0.53). The quality of life and the tolerability did not significantly differ between the two groups.

Conclusions. Alternative monotherapy or early treatment initiation with another AED drug resulted in similar efficacy, and the side effects associated with monotherapy and combined therapies were similar, which suggests that individual susceptibility is more important than the number and burden of AEDs used.

Key words: cluster-randomized, controlled trial, antiepileptic drug, guidelines

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The therapeutic strategy after the failure of the first antiepileptic drug (AED) in patients with epilepsy remains an issue. The rate of seizure recurrence in patients with partial seizures after initial treatment with one AED is relatively high, and seizure recurrence occurs in approximately 50% of patients (Schiller and Najjar, 2008). The rate of drug-resistant seizures is particularly high in patients with partial epilepsy (Semah and Ryvlin, 2005; Duncan *et al*., 2006).

Findings have emphasized the lack of efficacy of AED treatment in some patients, particularly patients with partial epilepsy (Semah *et al*., 1998; Kwan and Brodie, 2000a), despite the fact that over the last decade, there have been several new AEDs available for the treatment of epilepsy and some AEDs still under development (Bialer *et al*., 2013). After the failure of the first drug, there are two options: the use of an alternative AED (alternative monotherapy) or the use of an additional AED (early add-on therapy) (Kwan and Brodie, 2000b). All guidelines suggest that the initial therapeutic procedure in a patient with newly diagnosed epilepsy is to administer a single drug. During the last decade, after the failure of the first AED, most clinicians have typically administered another AED in place of the ineffective one; however, several authors have suggested that adding a second drug increases the chance of being seizure-free. However, this practice remains controversial and very few studies have evaluated this issue. In a study by Beghi *et al*., there was no significant difference between the two options (Beghi *et al*., 2003). Scottish guidelines have suggested that the strategy of early polytherapy could be the best option in order to increase the rate of seizure-free patients without any increase in drug-related side effects; this approach also remains controversial.

The rationale for our study was based on the differences between the guidelines on AED therapy for patients with epilepsy, in which the same strategy after failure of the first monotherapy is not recommended. In particular: (1) the latest French recommendations in which the prescription of a combination therapy is suggested, only after failure of at least two monotherapies (ANAES, 2004); and (2) the Scottish recommendations (Scottish Intercollegiate Guidelines network, *i.e*., SIGN, 2003) in which combination therapy is considered, when treatment with two first-line AEDs has failed or when the first well-tolerated drug substantially improves seizure control but fails to produce seizure-freedom at the maximal dosage (Scottish Intercollegiate Network, 2003).

In order to address this issue, we conducted a study in which the neurologists were randomised to either option, independently of the specific AED.

Materials and methods

A multicentre, cluster-randomised, prospective, controlled trial was designed. The original design of the study was previously published by our group (Ravaud *et al*., 2009). The unit of randomisation was care providers (neurologists) and the unit of analysis patients. This study followed the guidelines of the CONSORT statements for cluster-randomised controlled trials (Campbell *et al*., 2004) and non-pharmacological treatments (Boutron *et al*., 2008a; Boutron *et al*., 2008b). The trial was submitted to the National Commission on Personal Data (CNIL) in order to verify the personal data collection method, and this commission approved the trial. Informed consent for the study was obtained from all neurologists and patients, and all clinical investigations were conducted according to the principles expressed in the Declaration of Helsinki.

Patients

Care providers were neurologists, expert practitioners in France, who were consulted directly by patients without the need for referral. Neurologists were recruited by mail and received an invitation to participate in the trial; if interested, they responded by mail and were then contacted by phone and provided with more detailed information. Each neurologist included the first two patients who satisfied the following inclusion criteria:

– Ambulatory;
– Age 18 to 65 years old;
– Diagnosis of symptomatic or cryptogenic partial epilepsy according to the classification of epilepsy and epileptic syndromes by the International League Against Epilepsy, based on medical history, physical examination, EEG (electroencephalogram), and medical imaging (Commission, 1989);
– Partial epilepsy diagnosed less than five years ago;
– Treatment with an adequate AED used in monotherapy at suitable dosage;
– Never treated with any other AED;
– A minimum of two partial seizures (with or without secondary generalisation), despite AED treatment within the last three months prior to study selection, as documented by a seizure diary that was available for the three months before the study;
– Written consent for study participation.

The exclusion criteria were as follows: 1) a severe cardiovascular, renal or hepatic disease; 2) predictable lack of compliance; 3) history of psychiatric disease; 4) current psychiatric disorder; 5) regular use of

benzodiazepines for epilepsy; 6) surgical procedure scheduled during the trial follow-up; 7) degenerative neurological disease or cerebral tumour; and 8) pregnancy and/or breast-feeding.
The patients were blinded to the study hypothesis. They were informed that they were participating in a trial comparing the impact of two different guidelines developed by two different European governmental organisations. They were not informed about the content of the guidelines.

Study design

Neurologists who agreed to participate were randomly assigned to one of the two following treatment strategies:
1) Group A: alternative monotherapy;
2) Group B: add-on treatment.
Randomisation was stratified by region and was achieved by using a computer-generated process by a statistician who was not involved in the performance of the study, and worked at the Department of Epidemiology Biostatistics and Clinical Research, Hospital Bichat.
All randomised neurologists were invited to attend a preparatory meeting. During this meeting, the two procedures were presented to the two different groups: group A (alternative monotherapy) and group B (add-on treatment). The Scottish guidelines (Scottish Intercollegiate Guidelines network, SIGN, 2003) and the French recommendations (ANAES, 2004) were also presented to the neurologists.
In order to help the physician implement the treatment strategy, the guidelines were fully described in a case report form, which was carefully and accurately followed by the physician. If the physician did not wish to follow the guidelines, he/she was expected to provide reasons for non-compliance.
The prescription of cointerventions was at the care provider's discretion.

Outcomes

To assess outcomes, all patients who agreed to participate were evaluated by their neurologists during clinical visits at baseline (M0), Month 3 (M3), Month 6 (M6), and Month 12 (M12).

Primary outcome
The primary outcome was the percent of seizure-free patients within a two-month period (between the beginning of the fifth month of treatment and the end of the sixth month of the study). Each patient was expected to complete a card daily that was collected at each visit, on which patients had to record all their seizures.

Secondary outcomes
Secondary outcomes were as follows: 1) the number of seizure-free days during the two-month period, *i.e.* between the start of the fifth month of treatment and the end of the sixth month (ratio of the number of seizure-free days to the number of days within this period); 2) the percentage of patients achieving a 50% reduction of the number of seizures during a one-month period (*i.e.* the sixth month, compared with the number of seizures during the month before the inclusion that was determined retrospectively); 3) the quality of life, based on the Quality Of Life In Epilepsy (QOLIE 10) specific questionnaire and the Medical Outcomes Survey Short Form 12 (SF12), a generic quality-of-life questionnaire (Hurst *et al.*, 1998); and 4) tolerability (side effects based on patient questioning and clinical data).
All adverse events were systematically recorded. Severity was classified according to the World Health Organization classification. Investigators systematically reported all severe adverse events. Investigators assessed the relationship between intervention and adverse events.

Statistical analysis

A blinded statistician at the Department of Epidemiology Biostatistics and Clinical Research, Hospital Bichat, performed statistical analysis.
Analyses followed a pre-specified plan based on the principle of modified intent to treat (*i.e.*, all participants were included in the group to which they were assigned, regardless of whether they completed the intervention administered to the group). However, if no baseline data were recorded, the patients were excluded from the analyses. Data were analysed using SAS 9.1 (SAS institute Inc. Cary. NC, USA).

Results

Patients

The flow of clusters and individual patients through each stage is presented in *figure 1*.
A total of 143 neurologists were included between October and December 2004 and were randomised to group B (n=70) or group A (n=73). The last visit was performed in 2008, and all of the CRF corrections and analysis were obtained in 2011. Thirty-three neurologists were lost during follow-up at six months. Consequently, at six months, data were missing for 37 patients; 21 in group B and 16 in group A. As expected, most neurologists included 2 patients (n=136), other neurologists included 1, 3, 4, 5 or 6 patients (n=57, n=18, n=36, n=5, n=12, respectively). The data were available for 264 patients at M0, 223 patients at M3,

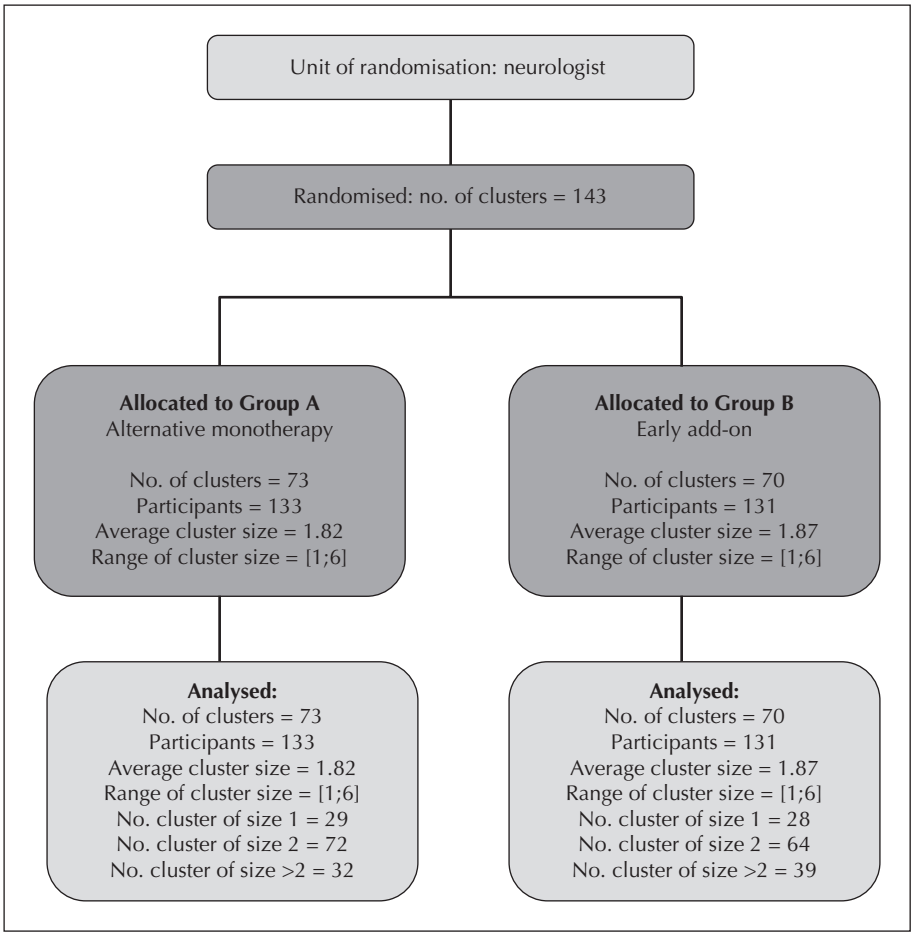

Figure 1. Flow diagram of the participants in the trial.

and 212 patients at M6. The baseline characteristics of the patients in each group are summarised in *table 1*. A summary of treatment for each group at the time of inclusion and at M0 is presented in *tables 2 and 3*, respectively.

Primary outcome

At six months, based on analysis of an intent to treat (patients with missing data were considered a failure), adjusted by the number of seizures at baseline, the primary outcome, *i.e.* the percent of seizure-free patients within the two-month evaluation period was 51% (68/132) in group A and 45% (59/131) in group B; p=0.34.

Secondary outcomes

The percentage of patients achieving a 50% reduction in the number of seizures during the sixth month (compared with the number of seizures during the month before the inclusion) was 76% (78/101) in group A and 84% (85/101) in group B; p=0.53.

The quality of life, assessed using the Quality Of Life In Epilepsy (QOLIE 10) specific questionnaire and the Medical Outcomes Survey Short Form 12 (SF12), did not differ between groups (*figure 2*, *table 4*).

Patients for whom at least one adverse event was recorded at M6 and patients who had a change in therapy due to insufficient tolerance were considered to have poor tolerance (failure). Other patients were considered to have a good tolerance (success). Patients lost during follow-up were considered to have poor tolerance (failure). Success was rated at 74% (n=86/116) in group A and 73% in group B (n=80/109) (p=NS).

It was not possible to evaluate the number of seizure-free days between the start of the fifth month of treatment and the end of the sixth month (ratio of the number of seizure-free days to the number of days within this period).

Discussion

Our results from this large, community-based, cluster-randomised, prospective, controlled trial indicate that, for patients with partial seizures after failure of the

Table 1. Baseline patient characteristics.

	Total *n*=264	Group A *n*=133	Group B *n*=131
Men/women, *n/n*	130/126	60/67	70/59
Age, Mean (SD) [*n*]; years	40.43 (14.8) [255]	42.14 (15.6) [124]	38.8 (13.8) [131]
Weight, Mean (SD) [*n*]; kg	71.1 (14.8) [253]	71.4 (15.1) [123]	70.9 (14.6) [130]
Height, Mean (SD) [*n*]; m	169.8 (9.1) [252]	169.0 (9.3) [122]	170.6 (8.8) [130]
Disease duration, Mean (SD) [*n*]; years	4.9 (6.05) [247]	5.0 (6.5) [121]	4.9 (5.6) [126]
Epilepsy aetiology, *n* (%)			
Missing data	9 (3.4)	7 (5.3)	2 (1.5)
Unknown	126 (47.7)	64 (48.1)	62 (47.3)
Genetic	2 (0.8)	1 (0.8)	1 (0.8)
Genetic and perinatal factors	1 (0.4)	0 (0.0)	1 (0.8)
Congenital malformation	22 (8.3)	11 (8.3)	11 (8.4)
Perinatal factors	6 (2.3)	2 (1.5)	4 (3.1)
Cranial injury	23 (8.7)	9 (6.8)	14 (10.7)
Cranial injury and surgery	5 (1.9)	1 (0.8)	4 (3.1)
Cerebral tumour	16 (6.1)	9 (6.8)	7 (5.3)
Cerebral surgery	4 (1.5)	3 (2.3)	1 (0.8)
Cerebral tumour and surgery	5 (1.9)	3 (2.3)	2 (1.5)
Degenerative disease	1 (0.4)	0 (0.0)	1 (0.8)
Cerebral vascular disease	22 (8.3)	13 (9.8)	9 (6.9)
Cerebral vascular disease associated with congenital malformation	1 (0.4)	1 (0.8)	0 (0.0)
Cerebral vascular disease and surgery	2 (0.8)	0 (0.0)	2 (1.5)
Cerebral infection	5 (1.9)	0 (0.0)	5 (3.8)
Cerebral infection and surgery	1 (0.4)	0 (0.0)	1 (0.8)
Other	13 (4.9)	9 (6.8)	4 (3.1)
Type of seizures			
Simple partial seizures	28 (10.6)	16 (12.0)	12 (9.1)
Complex partial seizures	41 (15.5)	25 (18.8)	16 (12.2)
Secondary generalised	81 (30.7)	39 (29.3)	42 (32.1)
Association of different types of seizures	106 (40.2)	46 (34.6)	60 (45.8)
Unclassified	4 (1.5)	3 (2.3)	1 (0.8)
Missing data	4 (1.5)	4 (3.0)	0 (0.0)
Number of seizures, median (IQR) [n] per month during the last 3 months [1]	2.3 (1.0-5.0) [253]	2.0 (1.0-4.3) [125]	2.3 (1.0-5.2) [128]

SD: standard deviation. Values in brackets are the number of patients with complete data.
[1]Two patients were excluded (one in each arm with extreme numbers of seizures per month during the last three months, of 100 and 110, respectively). In these two patients, the median (IQR)=2.0 (1.0-4.7) for group A and the median (IQR)=2.3 (1.0-5.3) for group B.

Table 2. Treatment at the time of inclusion in each group.

	Group				All	
	A (*n*=133)		B (*n*=131)		(*n*=264)	
	n	**%**	***n***	**%**	***n***	**%**
Missing data	5	3.8	-	-	5	1.9
Sodium valproate	52	39.1	37	28.2	89	33.7
Carbamazepine	13	9.8	31	23.7	44	16.7
Lamotrigine	14	10.5	21	16.0	35	13.3
Oxcarbazepine	17	12.8	16	12.2	33	12.5
Gabapentin	13	9.8	12	9.2	25	9.5
Phenobarbital	6	4.5	5	3.8	11	4.2
Topiramate	5	3.8	5	3.8	10	3.8
Phenytoin	2	1.5	2	1.5	4	1.5
Levetiracetam	2	1.5	2	1.5	4	1.5
Clobazam	3	2.3	-	-	3	1.1
Diazepam	1	0.8	-	-	1	0.4

first AED, alternative monotherapy or early addition of another AED result in the same rate of seizure-free patients. The theoretical advantage of an alternative monotherapy is based on the notion that AED side effects, which may be more frequent or severe with multiple AED usage, are minimised. The disadvantage of alternative monotherapy is that switching from one drug to another leads to a period of discontinuation of the first AED that could be a risk factor for seizure relapse. In contrast, one can also hypothesize that two drugs will be more powerful than one, leading to a benefit of the early add-on approach, in order to enhance the antiepileptic effect. Our study did not find any significant difference between these two options. The previous study by Beghi *et al*. with a smaller number of patients (*n*=157) also found no significant difference, and they suggested that a study to confirm this finding should be conducted (Beghi *et al*., 2003). This suggests that the physician, according to other criteria, may determine the choice of therapeutic strategy. The precise combination of AEDs was not determined in this study due to the fact that there were too many different drug combinations. Such a trial would be very useful but has never been performed using all the available AEDs since such a large number of patients is required. Other colleagues have suggested that rational polytherapy may be superior to non-rational polytherapy or a monotherapy (St Louis, 2009; French and Faught, 2009; Brodie and Sills, 2011).

After the failure of one AED, the chance of being seizure-free dramatically decreases (Schiller and Najjar, 2008). Schiller and Najjar reported that the response curve showing a greater than 50% reduction in seizure frequency corresponded to a mono-exponential function (Schiller and Najjar, 2008). This was one of the reasons leading the International League Against Epilepsy to revisit the definition of intractable epilepsy (Kwan *et al*., 2010). It was proposed that intractable epilepsy be defined as the failure of adequate trials, of two well-tolerated, appropriately chosen antiepileptic drug schedules (whether monotherapies or combination therapy), to achieve sustained seizure freedom (Kwan and Brodie, 2010).

A study conducted in Italy with 1,124 patients with refractory seizures, more than three quarters of whom were on polytherapy, demonstrated that side effects do not differ in patients administered monotherapy versus combination therapy. Adverse effects were not correlated to AED load, which probably reflects the ability of the practitioner to individually adjust each patient's treatment (Alexandre *et al*., 2010). The authors claimed that side effects are determined more

Table 3. Antiepileptic drug prescribed in each group at M0.

	Group				All	
	A (*n*=133)		B (*n*=131)		(*n*=264)	
	n	%	*n*	%	*n*	%
Missing data	6	4.5	0	0.0	6	2.3
Levetiracetam	48	36.1	6	4.6	54	20.5
Topiramate	16	12.0	0	0.0	16	6.1
Oxcarbazepine	15	11.3	1	0.8	16	6.1
Lamotrigine	21	15.8	1	0.8	22	8.3
Carbamazepine	14	10.5	0	0.0	14	5.3
Gabapentin	9	6.8	0	0.0	9	3.4
Valproate	4	3.0	0	0.0	4	1.5
Phenobarbital	0	0.0	1	0.8	1	0.4
Lamotrigine-Levetiracetam	0	0.0	18	13.7	18	6.8
Levetiracetam-Oxcarbazepine	0	0.0	16	12.2	16	6.1
Gabapentin-Levetiracetam	0	0.0	7	5.3	7	2.7
Levetiracetam-Valproate	0	0.0	31	23.7	31	11.7
Levetiracetam-Topiramate	0	0.0	4	3.1	4	1.5
Levetiracetam-Phenobarbital	0	0.0	4	3.1	4	1.5
Carbamazepine-Lamotrigine	0	0.0	3	2.3	3	1.1
Lamotrigine-Valproate	0	0.0	3	2.3	3	1.1
Carbamazepine-Valproate	0	0.0	3	2.3	3	1.1
Lamotrigine-Topiramate	0	0.0	2	1.5	2	0.8
Gabapentin-Oxcarbazepine	0	0.0	1	0.8	1	0.4
Gabapentin-Lamotrigine	0	0.0	1	0.8	1	0.4
Gabapentin-Valproate	0	0.0	1	0.8	1	0.4
Clobazam-Levetiracetam	0	0.0	1	0.8	1	0.4
Gabapentin-Topiramate	0	0.0	1	0.8	1	0.4
Levetiracetam-Phenytoin	0	0.0	1	0.8	1	0.4
Carbamazepine-Levetiracetam	0	0.0	25	19.1	25	9.5

Table 4. Quality of life in each group.

		Group A		Group B		*p values*		
		Mean	**SE**	**Mean**	**SE**	**Group**	**Trend**	***Interaction***
SF12 Mental	M0	40.68	0.94	40.35	1.07	0.4629	<0.0001	*0.7375*
	M3	44.56	0.84	43.58	1.06			
	M6	46.43	0.95	45.23	1.06			
SF12 Physical	M0	44.92	0.88	45.49	0.82	0.4165	<0.0001	*0.9841*
	M3	46.82	0.8	47.37	0.84			
	M6	47.36	0.8	48.47	0.78			
QOLIE10 Epilepsy Effects	M0	9.73	0.28	9.74	0.29	0.6427	0.1129	*0.9153*
	M3	9.32	0.34	9.54	0.32			
	M6	10.04	0.35	10.07	0.34			
QOLIE10 Mental Health	M0	9.49	0.12	9.48	0.13	0.4686	<0.0001	*0.5449*
	M3	11.78	0.21	11.36	0.26			
	M6	11.89	0.25	11.67	0.25			
QOLIE10 Role Function	M0	12.49	0.29	12.12	0.28	0.7731	<0.0001	*0.6001*
	M3	13.41	0.28	13.41	0.33			
	M6	13.8	0.32	13.65	0.37			

by individual susceptibility, type of drug used, and the skill of the practitioner than by the number and burden of AEDs used.

Our results have a high level of applicability because our neurologists were recruited in primary care settings, the inclusion and exclusion criteria were not too stringent, and the intervention, although complex, was easy to reproduce.

In trials assessing guideline implementations, the risk of contamination is high if physicians perform both interventions. Consequently, the performance of a cluster-randomised controlled trial avoids contamination. In cluster-randomised controlled trials, observations for individuals of the same cluster tend to be correlated. We controlled for the effect of clusters in the sample size calculation and statistical analyses. Nevertheless, such a trial implies a risk of selection bias, since, for our trial, neurologists were randomised to trial arms before including patients and were consequently aware of the treatment they had to provide to the included patients. Knowledge of patient assignment could lead to the exclusion of certain patients depending on their prognosis because they may have been allocated to an inappropriate group (Schulz and Grimes, 2002; Puffer *et al*., 2003). An issue involved in assessing non-pharmacological treatments is related to difficulties of blinding. Consequently, to limit the risk of bias, the patients were blinded to the study hypothesis (*i.e*. they were not informed of the type of treatment provided in the other group), as has been proposed in other trials (Boutron *et al*., 2004). Furthermore, patients in each arm had the same number of visits.

This study has several limitations and shortcomings. First, we did not achieve the expected sample size because of logistic difficulties in recruiting neurologists. We initially planned to include 400 neurologists, and two patients per neurologist. However, this goal was not achieved despite much follow-up correspondence. Our results remain meaningful, however, and they suggest that if a difference exists between these two options, the difference is very limited. Another

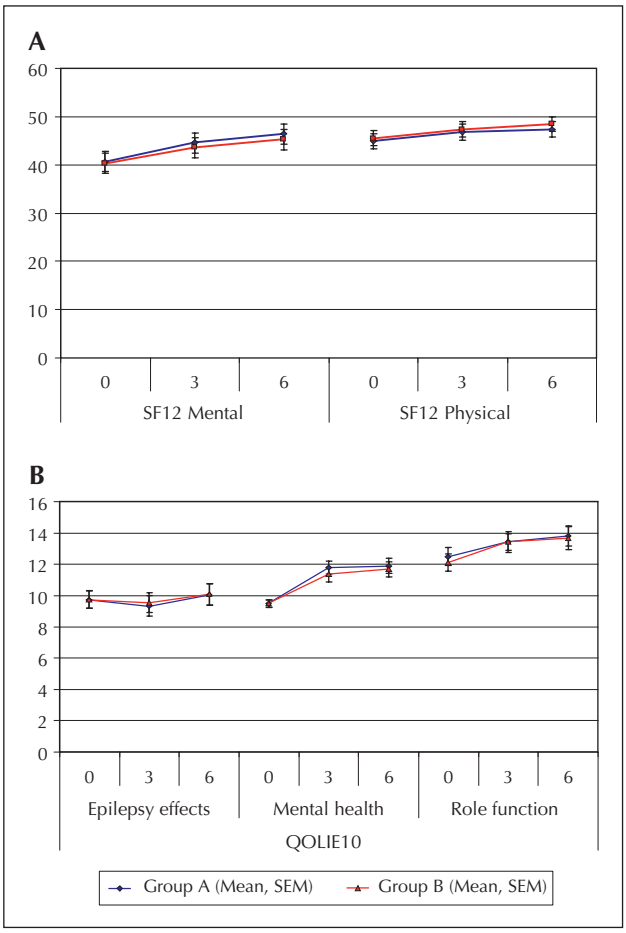

Figure 2. Health-related quality of life. A) SF 12. B) QOLIE 10.

limitation is the partial lack of blinding, and we cannot exclude that the study was influenced by subjective outcomes despite our attempt to limit the risk of bias by blinding the patients to the study hypothesis. Another possible shortcoming of the original design of this study is the duration of the observation period which was determined in order to evaluate the efficacy of the two strategies; one month is a very short period in which to evaluate a 50% reduction in seizure frequency.

Our study was not designed to investigate the role of each AED. Indeed, the choice of AED is a very important one, and in our study, the neurologists were asked to prescribe the most appropriate AED for each individual patient. The choice of an AED should be based on the efficacy and safety of each AED and the following other parameters: type of epileptic seizure; type of epilepsy syndrome; sex, age, and comorbidities of the patients; pharmacokinetics of the drug; drug interactions; the clinician's discretion; and national or international guidelines (Beghi, 2004; Chadwick and Marson, 2007; Stein and Kanner, 2009; Jobst, 2009; Perucca and Tomson, 2011). Among these criteria, the efficacy and tolerability should be the main criteria. The evaluation of efficacy of each drug should be based on clinical comparative trials. However, although there are many controlled clinical trials for each individual drug, there is very little data on direct comparisons between AEDs. A recent meta-analysis of randomised placebo-controlled trials of more recent AEDs suggested that the rate of patient response is not greater with new AEDs compared to older ones (Gao *et al*., 2013). Although there are numerous treatment options, up to 30% of patients with epilepsy do not undergo remission despite adequate treatment with an AED.

In conclusion, our study highlights that following failure of the first AED for patients with partial seizures, alternative monotherapy or early treatment initiation with another AED drug are two possible options, as previously suggested (Beghi *et al*., 2003). We did not find any differences in the efficacy and side effect profile between monotherapy and combined therapies, suggesting that individual susceptibility is more important than the number and burden of AEDs used. Despite the number of commercially available AEDs, it remains difficult to select the best option, and add-on treatment is not superior to changing to another AED. This suggests that in cases of refractory seizures after the first AED, the option of switching to another drug could be a very simple and effective choice. One may also argue for the need for very robust clinical drug trials, which could provide some scientific support for the best rational polytherapy.

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