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The long-term efficacy and safety of levetiracetam in a tertiary epilepsy centre

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ABSTRACT – *Aim*. To evaluate the long-term efficacy and safety of levetiracetam based on a large population of patients in a tertiary epilepsy centre. *Methods*. All patients who received levetiracetam at the Seoul National University Hospital between January 2007 and March 2009 were evaluated. Patients who underwent brain surgery for seizure control or who had associated progressive disease were excluded from this study. The electronic medical records of these patients were reviewed retrospectively. *Results*. A total of 568 patients were recruited, including 124 patients with generalised epilepsy. The mean duration of the follow-up period was 29.3 months. The seizure-free rate was 33.6% and was higher in patients with generalised epilepsy (51.6%) than patients with localisation-related epilepsy (28.6%). There was a strong correlation between initial response and dose-up response in 351 patients with increased dosage during the follow-up period. A total of 486 adverse events developed in 316 patients. The most common adverse event (24.3%) was irritability, which was associated with a high rate of drug discontinuation. Previous history of mood disorder was the only factor related to the development of irritability in patients using this medication. *Conclusion*. Levetiracetam was effective and safe as monotherapy and add-on therapy for partial and generalised epilepsy. The initial response to levetiracetam may provide useful information for predicting the response to increased dose of levetiracetam. However, the use of this medication was associated with a rate of irritability that was higher than expected in patients with a history of mood disorders.

Key words: levetiracetam, long-term, epilepsy, antiepileptic drug, irritability

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Epilepsy is a common neurological disorder which affects 1-2% of the global population across all age groups. The aim of epilepsy treatment is to achieve complete seizure control without causing any adverse events associated with disability. Although various antiepileptic drugs (AEDs) have been developed in the past few decades, 20-30% of patients may still fail to achieve seizure remission (Kwan *et al*., 2010).

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Levetiracetam (LEV) is a new AED with a novel mechanism of action. It binds to and modulates the synaptic vesicle protein 2A (Cereghino *et al*., 2000). LEV is rapidly and almost completely absorbed after oral administration and reaches a steady-state plasma level within two days after administration. It has linear pharmacokinetics with less than 10% protein binding and is not dependent on cytochrome P-450 isoenzyme for metabolism. It is fully excreted in urine, mostly in its uncharged form. It is also known not to interact with other medications (Patsalos, 2000).

The efficacy and tolerability of LEV as add-on therapy has been demonstrated for: localisation-related epilepsy (LRE) with or without secondary generalisation in adults (Cereghino *et al*., 2000; Shorvon *et al*., 2000; Wu *et al*., 2009), treatment-resistant partial-onset seizures in children aged 6-12 years (Glauser *et al*., 2002), myoclonic seizures in adults and adolescent above 12 years old with juvenile myoclonic epilepsy (Noachtar *et al*., 2008), primary generalised tonic-clonic seizures in adults and children above 6 years old with idiopathic generalised epilepsy (GE) (Berkovic *et al*., 2007), and refractory LRE and GE in adults (Betts *et al*., 2000), and in children with epilepsy above 6 months old (Lagae *et al*., 2005). LEV monotherapy has been shown to provide effective seizure control and is well tolerated in adults with newly diagnosed LRE or GE, without being any inferior to carbamazepine (Brodie *et al*., 2007), in children aged 4-16 years with newly diagnosed LRE or GE (Lagae *et al*., 2005), and children aged 5-13 years with childhood absence epilepsy or juvenile absence epilepsy (Verrotti *et al*., 2008).

However, it is difficult to generalise these findings regarding real-life clinical situations, as the inclusion and exclusion criteria of these studies were strictly defined. In addition, there is limited information on the long-term use of LEV with which to base clinical decisions upon, although several studies have reported the long-term efficacy and safety of LEV (Nicolson, 2004; Depondt *et al*., 2006; Bootsma *et al*., 2007). We therefore evaluated the long-term efficacy and safety of LEV based on a large population of patients at a tertiary epilepsy centre. The aim of this study was to determine the long-term efficacy of LEV, as well as its retention rates and adverse events in clinical practice.

Materials and methods

We screened the computerised database of the Seoul National University Hospital from January 2007 to March 2009 and recruited all patients who had been newly treated with levetiracetam to the study. Patients who underwent brain surgery for seizure control or who had associated progressive diseases were excluded from this study.

The medical records were reviewed for variables including age, gender, epilepsy syndrome, aetiology of epilepsy, electroencephalography (EEG) or 24-hour video-EEG monitoring (VEM), baseline seizure frequency, type of treatment, efficacy of treatment, the reason for discontinuation, and adverse events.

The baseline seizure frequency was defined as the frequency of seizures per month for partial and generalised tonic-clonic seizures, and the number of days of seizures for myoclonic seizures and absence seizures immediately prior to the prescription of LEV. The type of treatment was categorised into three groups: initial monotherapy, second monotherapy and polytherapy. The total daily dosage was identified for each initial, final and maximum dosage. The treatment efficacy was evaluated at the final visit and measured based on a five-point scale: seizure-free, rare, 75% reduction, 50% reduction, and not effective. Tolerance was defined as the decrease in efficacy after at least six months of seizure remission. If the LEV dose was changed, the treatment response was identified before and after the change of dose. The reason for LEV discontinuation was entered into the database using four criteria: not effective, side-effects, both, or other. Frequent adverse events were also recorded.

Statistical analyses were performed using SPSS 12.0KO software for Windows. Retention rates at one, two and three years were calculated using a life-table method. For efficacy outcome, treatment discontinuation, and adverse events, categorical variables were compared using the Student's *t* test or Fisher's exact test, and the χ^2 test; *p* values of ≤ 0.05 were considered to be statistically significant.

Results

Patient demographics

A total of 568 patients were recruited, including 124 (23.8%) patients with GE. The mean age was 32.99±12.69 years (range: 14-79 years) and of these, 275 (48.2%) were women. The mean duration of follow-up was 29.3±12.69 months (range: 1-60 months). Baseline seizures were more frequent in patients with LRE (3.37±5.03 days per month; range: 0-30 days per month) than in patients with GE (1.92±4.35 days per month; range: 0-30 days per month) (*table 1*). Of the 124 patients with GE, 53 patients (42.7%) had juvenile myoclonic epilepsy (JME), 60 (48.4%) had generalised tonic-clonic seizures (GTCS), five (4.1%) had absence seizures, and six (4.8%) had symptomatic GE. Generalised spikes and waves, or focal spikes and waves were seen in 82 of the 121 patients with GE who had received EEG or VEM. Of the patients with LRE, 256 patients (57.4%) had cryptogenic aetiology, 70 (15.7%)

Table 1. Baseline characteristics of the study population.

	Syndrome	No. of patients *n* (%)	Baseline seizure frequency	Treatment pattern		
				Initial monotherapy *n* (%)	Second monotherapy *n* (%)	Polytherapy *n* (%)
GE	JME	53 (9.3)	1.79 ± 3.58 (0-20)	14 (27.4)	14 (27.4)	25 (47.2)
	GTCS	60 (10.6)	1.13 ± 1.95 (0-15)	12 (20.0)	20 (33.3)	28 (46.7)
	Absence	5 (0.9)	0.50 ± 0.30 (0.2-1)	2 (40)	0	3 (60)
	Symp. GE	6 (1.1)	12.16 ± 12.35 (1-30)	0	0	6 (100)
	TOTAL GE	124 (23.8)	1.92 ± 4.35 (0-30)	28 (22.6)	34 (27.4)	62 (50.5)
LRE	Crypt. LRE	256 (45.1)	3.57 ± 5.58 (0-30)	19 (7.4)	28 (10.9)	209 (81.7)
	Symp. LRE	190 (33.5)	3.07 ± 4.17 (0-30)	12 (6.3)	10 (5.3)	168 (88.4)
	TOTAL LRE	444 (76.2)	3.37 ± 5.03 (0-30)	30 (6.8)	38 (8.6)	376 (84.6)
TOTAL	GE + LRE	568 (100)	3.05 ± 4.93 (0-30)	58 (10.2)	72 (12.7)	438 (77.1)

GE: Generalized Epilepsy; LRE: Localization Related Epilepsy; JME: juvenile myoclonic epilepsy; GTCS: generalised tonic clonic seizure; Symp: symptomatic; Crypt: cryptogenic.

had hippocampal atrophy or sclerosis, 36 (8.1%) had cortical malformation, 4 (0.9%) had vascular malformation, 16 (3.6%) had tumours, 5 (1.1%) had a history of stroke, 12 (2.7%) had a history of CNS infection, 3 (0.7%) had a history of perinatal problems, 9 (2.0%) had a history of trauma, and 35 (7.8%) had other causes. Focal epileptiform discharges were observed in 308 of the 429 patients with LRE who had received EEG or VEM. Fifty-eight patients (10.2%), including 28 with GE, were prescribed LEV as the initial monotherapy, and 72 patients (12.7%), including 34 with GE, were prescribed LEV as the second monotherapy. Patients who received polytherapy had taken 2.71±1.34 types of AEDs prior to add-on of LEV. Of 238 patients on polytherapy, 93 (21.2%), 124 (28.3%), 98 (22.4%) and 123 (28.1%) had taken one, two, three and four or more AEDs prior to add-on LEV, respectively. The mean dosage of LEV was 917.25±311.76 (range: 250-3,000) mg/day for the initial treatment and 1,253.30±609.68 (range: 125-3,000) mg/day at the last visit.

Efficacy

One hundred and ninety-one patients (33.6%) remained seizure-free during the follow-up period. The seizure-free rate was higher in patients with GE (51.6%) than in patients with LRE (28.6%). A >50% seizure reduction (defined as the responder rate) was achieved in 83.3% of the patients (90.3% of patients with GE and 82.0% of patients with LRE) (*figure 1A*). LEV was most effective for juvenile myoclonic epilepsy, with a 58.5% seizure-free rate and a 91.6% responder rate. Although the responder rate for 6 patients with symptomatic GE was 100%, there were no seizure-free cases. Tolerance was observed in 113 patients (20.8%).

Among the patients who received initial monotherapy, 60.7% GE and 60% LRE patients remained seizure-free, with a responder rate of 92.9 and 90%, respectively. Among the patients who received polytherapy, 43.5% GE and 24.2% LRE patients were seizure-free, with a responder rate of 88.7 and 80.3%, respectively. Although the seizure-free rate was significantly lower in patients who received polytherapy compared to those who received monotherapy for LRE, the responder rates were not significantly different between the second monotherapy and polytherapy groups for LRE and GE (*figure 1B, C*).

For LRE, the baseline seizure frequency was inversely correlated to seizure-free outcome (1.89±3.54 *vs.* 3.96±5.41 days/month; $p<0.001$) and the responder rate (3.01±4.61 *vs.* 5.00±6.42; $p=0.001$) (*table 2*). The number of prior AEDs was inversely correlated to the seizure-free outcome (2.08±1.04 *vs.* 3.09±1.37; $p<0.001$) and a seizure reduction rate of 75% (2.72±1.30 *vs.* 3.11±1.46; $p=0.009$), but not to a responder rate of 50%. In contrast, the baseline seizure frequency and the number of drugs were not associated with the efficacy of LEV for GE. Although the initial dose of LEV was not associated with efficacy, patients who did not become seizure-free took larger doses of LEV than the patients who had become seizure-free.

Initial and dose-up response

Three hundred and fifty-one patients (61.8%), including 68 with GE, received an increase in dosage for seizure control during the follow-up period. After

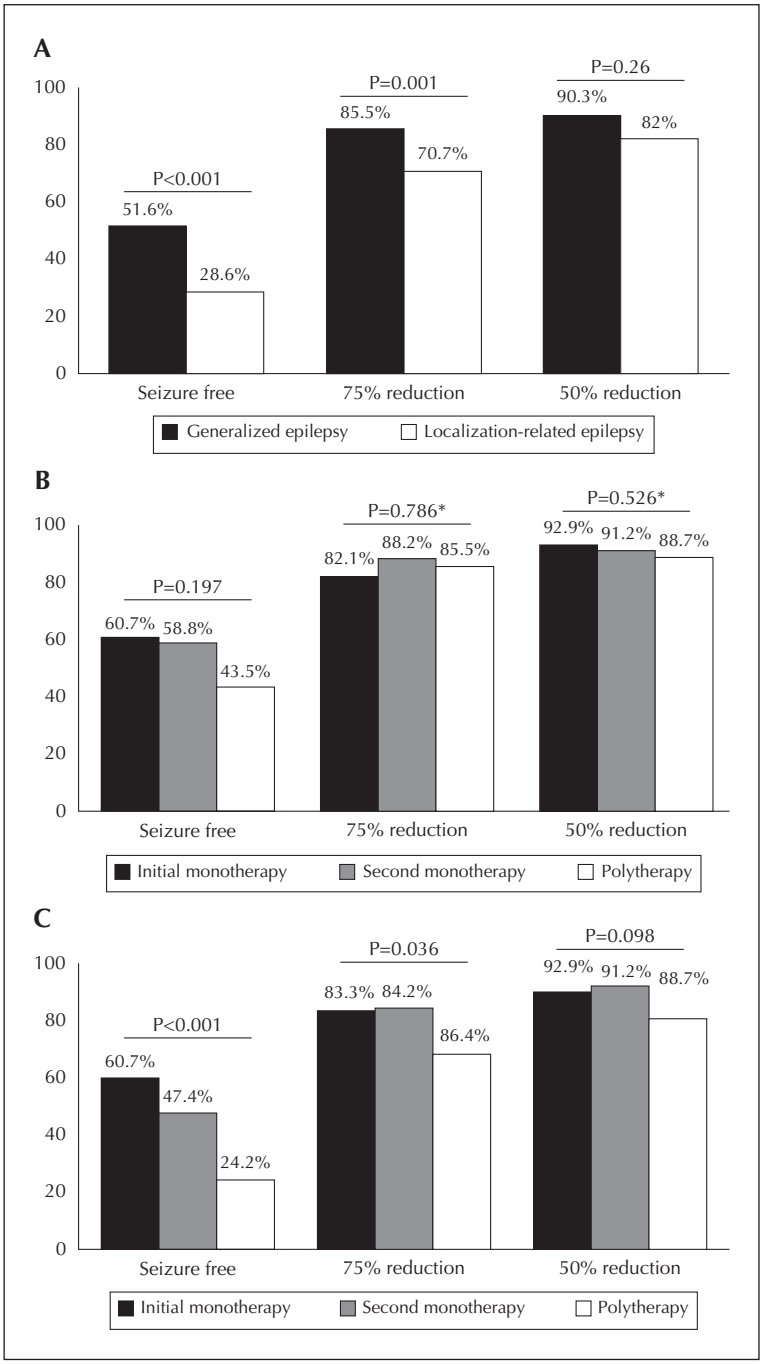

Figure 1. Efficacy of LEV according to epilepsy syndromes (A) and the relationship between treatment pattern and the efficacy of LEV in generalised epilepsy (B) and localisation-related epilepsy (C).
Pearson's χ^2 test and *linear by linear association were used for statistical analyses.

increasing the dose of LEV, the seizure frequency was reduced in 41 of 51 patients with GE (80.9%) and 129 of 201 patients with LRE (64.2%), with an initial response, whereas only 9 of 16 with GE (42.8%) and 31 of 83 with LRE (37.3%), without an initial response, exhibited a dose-up response (p=0.0009 and p<0.001, respectively). The initial response was not associated with the initial dose of LEV for both types of epilepsy.

Retention rate

The retention rates at one, two and three years were 78.7, 71.0, and 66.9%, respectively (*figure 2A*). The retention rates in patients with GE and LRE were not significantly different (p=0.1686) (*figure 2B*). Among the 568 patients included in this study, 177 patients (31.2%) dropped out (*table 3*). The LEV discontinuation

Table 2. Efficacy-related factors.

		Seizure free			75% reduction			50% reduction		
		(+)	(-)	*P* -value	Yes	No	*P* -value	Yes	No	*P* -value
GE	**Baseline seizure frequency** (day/month)	1.31±3.24	2.57±5.24	0.107	1.75±3.81	2.91±6.81	0.493	1.97±4.57	1.39±0.85	0.241
	No. of previous AEDs	1.81±0.83	2.00±0.87	0.402	1.89±0.89	2.11±6.01	0.471	1.89±0.87	2.14±0.69	0.467
	Initial dose (mg/day)	859.4±301.7	897.2±281.8	0.707	875.0±291.2	833.3±297.0	0.577	877.2±286.7	791.7±334.3	0.335
	Final dose (mg/day)	990.2±412.1	1,229.2±521.4	0.005	1,067.2±440.9	1,333.3±641.7	0.106	1,099.3±477.3	1,166.7±536.5	0.647
	Maximum dose (mg/day)	1,097.7±346.8	1,391.7±597.3	0.001	1,209.9±473.3	1,416.7±647.4	0.108	1,243.3±502.8	1,208.3±541.8	0.082
LRE	**Baseline seizure frequency** (day/month)	1.89±3.54	3.96±5.41	<0.001	2.75±4.54	4.86±5.84	<0.001	3.01±4.61	5.00±6.42	0.001
	No. of previous AEDs	2.08±1.04	3.09±1.37	<0.001	2.72±1.30	3.11±1.46	0.009	2.80±1.36	3.01±1.36	0.227
	Initial dose (mg/day)	891.7±328.2	946.4±310.5	0.100	918.8±329.8	959.6±279.8	0.186	952.8±318.7	953.1±305.8	0.485
	Final dose (mg/day)	1,023.6±465.5	1,403.0±661.9	<0.001	1,286.6±653.9	1,313.5±590.1	0.686	1,296.0±644.0	1,287.5±598.1	0.914
	Maximum dose (mg/day)	1,131.9±488.8	1,639.6±713.0	<0.001	1,447.5±692.6	1,607.7±691.1	0.027	1,484.9±697.6	1,537.5±686.8	0.541

Student's *t* test was used for statistical analysis.
GE: Generalized Epilepsy; LRE: Localisation Related Epilepsy.

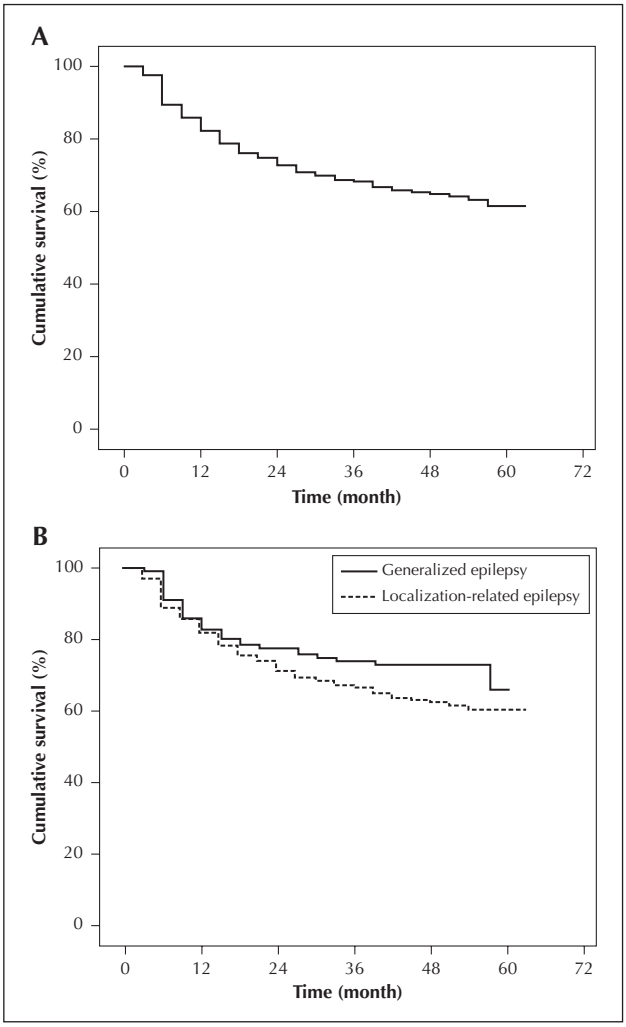

Figure 2. Retention curve illustrating the percentage of patients still being treated with LEV, as calculated using a life-table method. (A) Total study group. (B) Comparison between patients with generalised epilepsy and patients with localisation-related epilepsy.

rates did not significantly differ between the patients on monotherapy (37 of 130; 20.9%) and those on polytherapy (140 of 238; 32.0%; p=0.518). For 238 patients on polytherapy, the LEV discontinuation rates were 22.6, 30.6, 37.8, and 35.8% for patients who had received one, two, three or four or more types of AEDs prior to LEV, respectively (p=0.028). The main reasons for discontinuation were due to side effects (31.1%) and lack of efficacy (32.2%). Four patients, including two patients with GE, discontinued treatment after seizure remission.

Adverse events

A total of 486 adverse events were recorded in 316 patients (55.6%), and of these patients, 126 (22.2%) experienced two or more adverse events. Common adverse events were irritability (24.3%), dizziness (20.1%), headache (11.8%), and somnolence (11.6%) (*table 4*). Irritability, somnolence, and psychosis were associated with a high rate of drug discontinuation. Fourteen of the 34 patients (41.2%) who had a history of mood disorders developed irritability (p=0.018). Psychosis occurred in 6 patients (1.1%) and was significantly associated with a history of psychosis (2 of 10 patients; p=0.004) and a history of cognitive impairment (3 of 59 patients; p=0.017). The baseline seizure frequency, dose of LEV, dose-escalation rate to the maximum dosage, and the number of prior AEDs were not associated with any adverse events.

Discussion

This study is a retrospective study of LEV based on a large population (n=568) with a long follow-up period (mean: 29 months; maximum: 60 months) in a tertiary epilepsy centre. As all patients who were newly treated with LEV during the period from January 2007 to March 2009 were included in this study, the risk of selection bias was low. Thus, these results may be a good reflection of the actual clinical setting. In a previous large retrospective study with long-term treatment with LEV and a follow-up period of 24 months, only 301 patients with refractory epilepsy were enrolled, among whom 32.6% had mental impairment (Bootsma *et al*., 2007).

Table 3. Reasons for discontinuation of levetiracetam.

	Total (n=568)	Generalised epilepsy (n=124)	Localisation-related epilepsy (n=444)
Not effective *n* (%)	57 (10.0)	7 (5.6)	50 (11.3)
Side effects *n* (%)	55 (9.7)	10 (8.1)	45 (10.1)
Both *n* (%)	11 (1.9)	1 (0.8)	10 (2.3)
Others *n* (%)	50 (8.8)	13 (10.5)	37 (8.3)
Tapering *n* (%)	4 (0.7)	2 (1.6)	2 (0.5)
Total *n* (%)	177 (31.2)	33 (26.6)	144 (32.4)

Table 4. Adverse events during levetiracetam therapy.

Adverse event	**Frequency** ***n*** **(%)**	**Drug discontinuation** ***n*** **(%)**	*p* value
Irritability	138 (24.3)	28 (50.9)	<0.001
Dizziness	114 (20.1)	12 (21.8)	0.733
Headache	67 (11.8)	7 (12.7)	0.822
Somnolence	66 (11.6)	16 (29.1)	<0.001
Depression	39 (6.9)	7 (12.7)	0.087
General weakness	26 (4.6)	4 (7.3)	0.304
Gastrointestinal problem	18 (3.2)	4 (7.3)	0.086*
Psychosis	6 (1.1)	5 (9.1)	<0.001*
Rash	2 (0.4)	0	>0.999*
Others	10 (1.8)	2 (3.6)	0.251*
Total	316 (55.6)	55 (100)	

Pearson's χ^2 test and *Fisher's exact test were used for statistical analyses.

LEV was very effective in controlling seizures in 128 patients with GE, 51.6% of whom achieved seizure freedom, and yielded a 50% responder rate of 90.3%. The seizure-free and responder rates were higher in patients receiving monotherapy (60.7 and 92.9%, respectively) compared with those receiving polytherapy (48.5 and 88.7%, respectively), although this result was not statistically significance (p=0.197 and p=0.521, respectively). In a retrospective study of 59 patients who received LEV monotherapy over 12 months, the seizure-free rate and 50% responder rate were lower, at 54.2 and 74.5%, respectively (Stephen *et al*., 2011). Previous randomised controlled trials have shown that adjuvant treatment with LEV in patients with GE was effective in controlling myoclonic seizures (25% were seizure-free and 58.3% had >50% seizure reduction during a 16-week period) (Noachtar *et al*., 2008) and generalised tonic-clonic seizures with refractory idiopathic GE (34.2% were seizure-free and 72.2% had >50% seizure reduction during a 20-week period) (Berkovic *et al*., 2007). In our study, LEV was most effective in achieving seizure freedom in cases of juvenile myoclonic epilepsy (58.6%; 31 of 53 cases). LEV was also effective in treating symptomatic GE, in which all six patients exhibited >50% seizure reduction.

LEV was also effective in controlling seizures in the 444 patients with LRE in this study. However, their seizure-free rate was 28.6%, which was significantly lower than that observed in patients with GE (51.6%). This difference may be explained by the fact that a greater number of patients with LRE received polytherapy compared to patients with GE (77.1% *vs*. 50.5%). From another retrospective study of LEV monotherapy, it was shown that the seizure-free rates in LRE and GE patients were 44.6% (75 of 161) and 54.2% (32 of 59), respectively (Stephen *et al*., 2011). The seizure-free rates for LRE decreased in order of first monotherapy, second monotherapy and polytherapy (60% *vs*. 47.4% *vs*. 24.2%, respectively; p<0.001). The responder rate was 83.3% and this did not significantly correlate with treatment patterns. Another previous randomised controlled trial showed a similar efficacy of LEV monotherapy in adult patients, with a seizure-free rate of 56.6% and a responder rate of 86.0% over one year (Brodie *et al*., 2007). Conversely, four randomised controlled trials in patients with partial-onset seizures treated with LEV as add-on therapy reported seizure-free rates ranging between 5.0 and 10.8% and a 22.8-55.9% 50% seizure reduction (Ben-Menachem and Falter, 2000; Cereghino *et al*., 2000; Shorvon *et al*., 2000; Wu *et al*., 2009). This difference can be explained by the different characteristics of the patients enrolled in each of the studies. These trials only enrolled patients with refractory partial seizures for adjuvant therapy, whereas, in contrast, our study may have included non-refractory patients in the group that received polytherapy.

Previous studies have shown that a high seizure frequency prior to AED treatment, including LEV, indicates a poor prognosis (Collaborative Group for the Study of Epilepsy, 1992; Sillanpaa, 1993; Stephen *et al*., 2011). In our study, the baseline seizure frequency and the number of other AEDs, when taking LEV as an adjuvant treatment, were predictors of LEV efficacy for LRE, but not for GE. Although the final and maximum dose of LEV were much higher in non-seizure-free patients than they were in seizure-free patients, a 75% or 50% seizure reduction did not correlate with these parameters. A recent meta-analysis has shown that the individual dose of LEV may not be associated with drug efficacy (Mbizvo *et al*., 2012).

In this study, 351 patients (61.8%), including 68 with GE, received an increase in dosage for seizure control

during the follow-up period and there was a strong correlation between the initial response and the dose-up response for both types of epilepsies. Moreover, the individual dose of LEV did not affect the initial response. These results suggest that the initial response of LEV, and not the dosage itself, may provide useful information for predicting future response with increased dose of levetiracetam.

The retention rates, calculated here using a life-table method, were 78.77% at one year and 66.9% at three years, and there was no significant difference between GE and LRE. Previous studies have reported similar or lower retention rates of 65-74% after one year and 45-58% after two years (Bootsma *et al*., 2007; Nicolson, 2004). Results from a large epilepsy cohort showed a 58% retention rate at three years (Depondt *et al*., 2006), which was higher than those for other new AEDs (retention rates of 30% for topiramate, 29% for lamotrigine and <10% for gabapentin at three years) obtained for patients from the same epilepsy clinics (Lhatoo *et al*., 2000). In our study, a higher number of previous AEDs was more likely to lead to LEV discontinuation. A previous large epilepsy cohort study has shown that the hazards of adverse events related to LEV discontinuation were increased by 1.2 fold (95% CI: 1.03-1.44) for each concurrent AED (Depondt *et al*., 2006).

Of the total of 568 patients included in the study, 177 patients dropped out and the main reasons for discontinuation were due to adverse events (9.7%) and lack of efficacy of LEV (10.0%). The adverse events, which were associated with a high rate of drug discontinuation, were irritability, somnolence, and psychosis. Five of 6 patients with drug-related psychosis discontinued LEV. A previous history of psychosis or cognitive problems was associated with the development of psychosis. A meta-analysis of LEV has shown that the baseline regimen of AED did not appear to increase the side effects that were attributable to LEV (Lo *et al*., 2011). Although we did not collect data on the baseline AED regimen, the number of previous AEDs did not affect the adverse events of LEV in our study.

Irritability (24.3%) was one of the most common adverse events in our study with rates higher than we had expected. Irritability was defined in a patient who demonstrated greater than moderate aggression or hostility according to the Brief Psychiatric Rating Scale (Ventljra *et al*., 1993). A randomised, double-blind, placebo-controlled trial of LEV, for the treatment of GTCS in patients with idiopathic GE, reported that irritability developed in 5.1% of patients during a 24-week period (Berkovic *et al*., 2007). Although not all trials reported the same adverse events, a recent meta-analysis of LEV add-on therapy for drug-resistant LRE showed that the behavioural adverse events affected 4.54% of the patients (RR compared to placebo 1.87; 95% CI: 1.19 to 2.95) and this was more frequent in children (22.64%, RR 1.90; 95% CI: 1.16-3.11) than in adults (1.04%, RR 1.79; 95% CI: 0.59-5.41). Moreover, it was found that no individual behavioural adverse event affected more than 1% of patients, including irritability, hostility, and aggression (Mbizvo *et al*., 2012). In an open-label trial of LEV add-on therapy for refractory LRE in 1,541 patients, the most frequent psychiatric adverse events were: depression (37 patients; 2.4%), aggression (30; 1.9%), and irritability (27; 1.8%) (Steinhoff *et al*., 2007). Of the 228 patients in a recent observational study of LEV monotherapy for a median duration of 12 months, 7 (3.1%) cases of intolerable aggression and 2 cases (0.9%) of irritability developed (Stephen *et al*., 2011). The long-term follow-up period of our study may explain the high incidence of irritability. The baseline seizure frequency, dose titration rate, or history of cognitive impairment were not found to be associated with irritability. A history of mood disorder was the only factor related to the development of irritability in our study.

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