ORIGINAL ARTICLE

Levetiracetam in Clinical Practice: Efficacy and Tolerability in Epilepsy

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ABSTRACT: ***Background:*** The aim of this study was to evaluate efficacy and tolerability of levetiracetam (LEV) in patients with different epilepsy syndromes. ***Methods:*** We evaluated epileptic patients seen in the previous 18 months, including all patients with present or past exposure to LEV. Tolerability of LEV therapy was evaluated in all patients; efficacy was evaluated only in patients who had received LEV for at least six months. Two hundred and two patients were included in the study. Patients were considered responsive when showing a > 50% reduction in seizures frequency and non-responders when seizure frequency was unchanged, worsened or showed a reduction < 50%. ***Results:*** Thirty patients did not complete six months of LEV treatment and dropped out. 57.4% of the patients with uncontrolled seizures treated for at least six months were responders, with 27.7% seizure free. Adverse effects were observed in 46 patients (23%) and were responsible for early drop out in 26. Adverse effects occurred significantly more often in females than in males (30.6% vs 13.2%); moreover, nearly 30% of women with adverse effects complained of more than one adverse effect, while this was never observed in male patients. ***Conclusions:*** Our study shows LEV as a well tolerated and effective treatment, both in monotherapy and as an add-on. Further investigations on larges samples are needed to investigate the issue of gender-related tolerability.

RÉSUMÉ: Efficacité et tolérance du lévétiracétam dans l'épilepsie en pratique clinique. ***Contexte :*** Le but de cette étude était d'évaluer l'efficacité et la tolérance du lévétiracétam (LEV) chez les patients qui sont atteints de différents syndromes épileptiques. ***Méthodes :*** Nous avons évalué les patients épileptiques qui ont consulté au cours des 18 derniers mois et nous avons inclus dans l'étude tous les patients qui avaient déjà pris ou qui prenaient le LEV. La tolérance au traitement par le LEV a été évaluée chez tous les patients ; l'efficacité a été évaluée seulement chez les patients qui avaient pris du LEV pendant au moins six mois. Deux cent deux patients ont été inclus dans l'étude. Les patients étaient considérés comme des répondeurs quand la fréquence de leurs crises avait diminué de plus de 50 % et comme des non-répondeurs quand la fréquence des crises n'était pas modifiée, avait augmenté ou diminué de moins de 50 %. ***Résultats :*** Trente patients n'ont pas complété les six mois de traitement et ont été retirés de l'étude. Parmi les patients qui avaient des crises non maîtrisées et qui ont été traités pendant au moins 6 mois, 57,4 % étaient des répondeurs et 27,7 % n'avaient plus de crises. Des effets indésirables ont été observés chez 46 patients, soit 23 %, et ont motivé un abandon précoce du traitement chez 26 patients. Les effets indésirables étaient significativement plus fréquents chez les femmes que chez les hommes, soit chez 30,6 % contre 13,2 % ; de plus, environ 30 % des femmes qui ont eu des effets indésirables se sont plaintes de plus d'un effet indésirable alors que ceci n'a pas été observé chez les hommes. ***Conclusions :*** Notre étude démontre que le LEV est un traitement bien toléré et efficace, tant en monothérapie que comme traitement adjuvant. Il faudra procéder à des études comportant un nombre plus grand de patients pour évaluer la tolérance reliée au sexe.

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Levetiracetam (LEV) is a new antiepileptic drug (AED) indicated as adjunctive therapy in the treatment of partial seizures and primary generalized seizures. Both initial clinical trials and post-release clinical experience[1-3] show that previously drug resistant epileptic patients may be rendered seizure free with add-on therapy with LEV. In two recent studies examining LEV efficacy on drug resistant patients in everyday clinical practice, 16.3% and 10% respectively achieved seizure freedom after addition of LEV therapy[4,5]. Recent studies suggest LEV efficacy also as monotherapy in new-onset partial epilepsy and idiopathic generalized epilepsy[6,7]. Because of its favorable pharmacokinetic profile, LEV is particularly suitable for special populations (such as elderly patients, patients with cognitive problems, patients with treated co-morbidities) in which traditional AEDs are often poorly tolerated because of drug-to-drug interactions, negative impact on cognitive function, toxicity on liver function[8,9].

The aim of this study was to evaluate LEV efficacy and tolerability in a setting of clinical practice. We carried out a retrospective evaluation of patients seen in our institutions who had been treated with LEV both as add-on and monotherapy.

Study design: After a retrospective evaluation of all patients with epilepsy seen in our outpatients facilities in the last 18 months, we included in this study all patients with present or past exposure to LEV, independently from duration of LEV therapy. Tolerability of LEV therapy was evaluated in all

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patients, while efficacy of LEV treatment was evaluated only in patients who had received LEV for at least six months after titration. Demographic and clinical data were evaluated retrospectively from clinical charts; seizure frequency was evaluated from patients' diaries, a tool that all our patients in our service are instructed to employ. Patients and/or caregivers note every seizure in a diary, indicating clinical features and, when present, precipitating factors. The examining doctor collects this information at every appointment and writes it down in the patient's chart. For the purpose of this study, seizure frequency in the six months preceding LEV treatment was considered as baseline; for patients with newly diagnosed epilepsy, baseline was obtained by dividing the total number of seizures presented since the onset of epilepsy by the months of epilepsy duration at study entry. All patients with newly diagnosed epilepsy included in this study had epilepsy duration of at least four months at study entry.

Material: Two hundred-two patients met the inclusion criteria and were included in the study (Table 1). Ninety-one were males and 111 females, ranging in age from 7 to 93 yrs. One hundred forty-six patients were affected by focal epilepsies and 56 by generalized epilepsies; in particular 48 patients were affected by Idiopathic Generalized Epilepsy (IGE), 8 patients by Symptomatic Generalized Epilepsy (SGE), 2 patients by Idiopathic Focal Epilepsy (IFE), 57 by Cryptogenic Focal Epilepsy (CFE) and 87 by Symptomatic Focal Epilepsy (SFE). Thirty of these 202 patients (14.8%) dropped out of the study before completing six months of LEV treatment, because of adverse effects in 26 and worsening of seizures in 4. Consequently, efficacy of LEV treatment was evaluated only in 172 patients treated with LEV for at least six months, which for the purpose of analysis were subdivided in three groups:

- **Controlled Seizures Group:** These 31 patients had already achieved complete seizure control with previous AED therapy but reported adverse effects related to treatment; in these subjects LEV was introduced with the aim of reducing or withdrawing previous AED treatment.
- **De Novo Group:** These 19 patients had newly diagnosed epilepsy which had never been treated; LEV was used as first line drug because of its favorable profile.
- **Drug Resistant Group:** These 122 patients had drug resistant seizures and received LEV with the aim of improving seizure control.

Patients were considered responsive when showing relevant improvement with LEV treatment; in particular, they were considered seizure free when achieved seizure freedom and responders when they showed a $> 50\%$ but $< 100\%$ reduction in seizures frequency. Patients were considered non-responders when seizure frequency was unchanged, worsened or showed a reduction of $\leq 50\%$. Response to LEV therapy was evaluated separately in Controlled Seizures, De Novo and Drug Resistant Groups. Moreover, in the Drug Resistant Group response to therapy was evaluated separately according to epilepsy type.

Statistical analysis: Statistical analysis was performed by Dianthus Medical using STATA version 11. Both tolerability and efficacy were analyzed by logistic regression, performing univariate and multivariate analyses. For tolerability, the presence of adverse effects was considered as the outcome, and univariate logistic regression analysis was performed for the following variables: age, sex, epilepsy type (focal or generalized), LEV monotherapy, number of concomitant AEDs, LEV daily dose, LEV plasma levels. Two multivariate logistic regression analyses were performed in the analysis of tolerability, the first including only age, sex and LEV daily dose, and the second including all predictor variables except for LEV plasma levels which had many missing values. Statistical analysis of efficacy was performed only in the Drug Resistant Group which was the most numerous, while the others two were quite small. Since efficacy had three possible outcomes (non-

Table 1: Demographic data of study population

Study population (202 patients)	
Epilepsy Type	*Focal:* 146 (72.3 %) *Generalized:* 56 (27.7 %)
Sex	*M:* 91 (45.0 %) *F:* 111 (55.0 %)
Age	*Range:* 7-93 *< 10:* 2 (1.0 %) *10-24:* 34 (16.8 %) *25-39:* 67 (33.2 %) *40-54:* 56 (27.7 %) *55+:* 43 (21.3 %)
Average seizures prior to LEV (per month)	5.5
Patients receiving LEV for ≥6 months (172 patients subdivided in 3 groups)	
A) Controlled Seizures Group (31 patients)	
Epilepsy Type	*Focal:* 20 (64.5 %) *Generalized:* 11 (35.5 %)
Sex	*M:* 19 (61.3 %) *F:* 12 (38.7 %)
Age	*Range:* 7-79 *< 10:* 1 (3.2 %) *10-24:* 6 (19.4 %) *25-39:* 7 (22.6 %) *40-54:* 12 (38.7%) *55+:* 5 (16.1 %)
Average seizures prior to LEV (per month)	0
B) De Novo Group (19 patients)	
Epilepsy Type	*Focal:* 13 (68.4 %) *Generalized:* 6 (31.6 %)
Sex	*M:* 8 (42.1 %) *F:* 11 (57.9 %)
Age	*Range:* 10-93 *< 10:* 0 (0%) *10-24:* 4 (21.1 %) *25-39:* 5 (26.3 %) *40-54:* 2 (10.5 %) *55+:* 8 (42.1 %)
Average seizures prior to LEV (per month)	3.6
C) Drug Resistant Group (122 patients)	
Epilepsy Type	*Focal:* 90 (73.8 %) *Generalized:* 32 (26.2 %)
Sex	*M:* 57 (46.7 %) *F:* 65 (53.3 %)
Age	*Range:* 9-81 *< 10:* 1 (0.8 %) *10-24:* 19 (15.6 %) *25-39:* 49 (40.1 %) *40-54:*34 (27.9 %) *55+:* 19 (15.6 %)
Average seizures prior to LEV (per month)	7.8

responder, responder, seizure-free), ordinal logistic regression was performed. In particular, univariate logistic regression analysis was performed for the following variables: age, sex, epilepsy type (focal or generalized), LEV monotherapy, presence of abnormal magnetic resonance imaging (MRI) findings, history of surgery for epilepsy or being candidate to surgery for epilepsy, history of status epilepticus, adverse effects to LEV, number of concomitant AEDs, LEV daily dose, LEV plasma levels. In order to fully examine the relationships among possible outcomes and predictor variables, several multivariate analyses were performed: the first included only age, sex and LEV daily dose; the second included age, sex and all significant univariate predictors except LEV plasma levels; the third included age, sex and all significant univariate predictors except LEV plasma levels, LEV daily dose and number of concomitant drugs; the fourth included all predictors except LEV plasma levels; the fifth included all predictors except LEV plasma levels, LEV daily dose and number of concomitant drugs. $P < 0.05$ was considered significant.

Results

Tolerability

Adverse effects were observed in 46 patients out of 202 patients (23%) and led to LEV withdrawal in 32 (16%); 26 of these 32 patients dropped out before completing six months of LEV treatment. Several patients (pts) complained of more than one adverse effect: the most frequent complaints were drowsiness (16 pts), irritability (9 pts), asthenia (8 pts), gastric discomfort (5 pts). More rarely, patients complained of insomnia (2 pts), skin rash (2 pts), depression (2 pts), headache (2 pts), severe behavioral disturbances (2 pts). Occasional complaints,

Table 2: Tolerability analysis (logistic regression) in 202 patients

Univariate analyses

Adverse effects and age groups	**Odds Ratio**	**P value**	**[95% Conf. Interval]**
25-39 vs < 25	1.195055	0.728	.4371845 3.266713
40-54 vs < 25	1.12987	0.819	.3980047 3.207516
55+ vs < 25	1.603687	0.383	.5551657 4.63251
Adverse effects and sex	**Odds Ratio**	**P value**	**[95% Conf. Interval]**
Males vs Females	.344006	0.004 *	.165925 .7132145
Adverse effects and epilepsy type	**Odds Ratio**	**P value**	**[95% Conf. Interval]**
Focal vs generalized	1.546667	0.225	.7640764 3.13081
Adverse effects and LEV monotherapy	**Odds Ratio**	**P value**	**[95% Conf. Interval]**
Monotherapy vs polytherapy	.6862974	0.330	.3218739 1.463319
Adverse effects and # of concomitant AEDs	**Odds Ratio**	**P value**	**[95% Conf. Interval]**
# of AEDs	1.165841	0.360	.8396073 1.618835
Adverse effects and LEV daily dose	**Odds Ratio**	**P value**	**[95% Conf. Interval]**
LEV daily dose	.3389807	0.000 *	.2280538 .5038632
Adverse events and LEV plasma levels	**Odds Ratio**	**P value**	**[95% Conf. Interval]**
LEV plasma levels	.9236566	0.026 *	.8612183 .9906218

Multivariate analyses

Analysis of age, sex, and LEV daily dose

	Odds Ratio	**P value**	**[95% Conf. Interval]**
25-39 vs < 25	1.858417	0.289	.5906434 5.847378
40-54 vs < 25	1.967771	0.268	.5935093 6.524117
55+ vs < 25	1.051193	0.934	.3199658 3.453517
Males vs Females	.395395	0.024 *	.1770108 .8832071
LEV daily dose	.3226768	0.000 *	.2100059 .4957973

Analysis of all predictors (except LEV plasma levels)

	Odds Ratio	**P value**	**[95% Conf. Interval]**
25-39 vs < 25	1.549828	0.461	.4836615 4.966214
40-54 vs < 25	1.758903	0.379	.4994396 6.194421
55+ vs < 25	1.075523	0.908	.3143022 3.680372
Males vs Females	.4271239	0.043 *	.1872661 .9742011
LEV daily dose	.3057452	0.000 *	.1982331 .4715666
Focal vs Generalized	1.522422	0.338	.6441175 3.598362
Monotherapy vs Polytherapy	.6184629	0.493	.1563363 2.446625
# of concomitant AEDs	1.239282	0.497	.6672554 2.301699

• Statistically significant

Table 3: Efficacy: summary of results on 172 patients subdivided in three groups

Controlled Seizures Group (31 patients)	
Average number of AEDs associated to LEV	0.354
Patients receiving LEV monotherapy	22 (71.0%)
Response to LEV	Non-Responders: 1 (3.2%) Responders: 0 Seizure Free: 30 (96.8%)
De Novo Group (19 patients)	
Average number of AEDs associated to LEV	0
Patients receiving LEV monotherapy	19 (100%)
Response to LEV	Non-Responders: 2 (10.5%) Responders: 6 (31.6%) Seizure-Free: 11 (57.9%)
Drug Resistant Group (122 patients)	
Average number of AEDs associated to LEV	1.598
Patients receiving LEV monotherapy	12 (9.8%)
Response to LEV	Non-Responders: 58 (47.5%) Responders: 36 (29.5%) Seizure-Free: 28 (23.0%)

Non-Responders: patients in whom seizure frequency was unchanged, worsened or showed a reduction ≤ 50% after LEV was introduced; Responders: patients in whom seizure frequency showed a reduction > 50%, but were not seizure-free, after LEV was introduced; Seizure free: patients who became seizure-free (De Novo Group and Drug Resistant Group) or preserved seizure freedom (Controlled Seizures Group) after LEV was introduced.

reported by one patient each, were diarrhea, vomiting, weight-loss, dizziness, memory disturbances, tremor, pruritus and visual disturbances.

Statistical analysis (Table 2) showed no significant association of adverse effects with age groups, epilepsy type (focal or generalized), percentage of monotherapy patients, number of concomitant AEDs. There was a significant association with sex, in particular with adverse effects associated with female patients. In particular, adverse effects were reported in 34 out of 111 female patients (30.63%) and in 12 out of 91 male patients (13.19%). Moreover, adverse effects were significantly associated with low daily doses of LEV and with low LEV plasma levels. It must be underlined that LEV plasma levels were obtained only in 123 patients out of 202.

Efficacy

Results of the efficacy study are summarized in Table 3.

The 31 patients of the Controlled Seizures Group were already seizure free and received LEV in order to reduce or withdraw previous AED treatment, responsible of adverse effects (impaired libido, menstrual disturbances, tremor, liver function impairment, dizziness, behavioral disturbances, mood changes, cognitive impairment, etc.). Most of these patients (20 out of 31) were affected by focal epilepsies with complex partial seizures and/or simple partial seizures, occasionally with secondary generalization. The remaining 11 had generalized epilepsies with absences and/or myoclonic seizures and/or tonic-clonic generalized seizures. Twenty-two of these 31 patients (71.0%) were switched to LEV monotherapy while in the remaining nine LEV was given as add-on treatment with reduction of concomitant AEDs. After this therapy change, 30/31 patients (96.8%) preserved seizure freedom, while one patient with focal epilepsy, who had been switched from Phenobarbital to LEV, had a recurrence of seizures (a single focal seizure with secondary generalization). In all patients of this group the withdrawal or reduction of previous AED therapy was accompanied by improvement or disappearance of previously reported adverse effects. However, four patients in this group reported new side effects (irritability in two, drowsiness in two) after treatment with LEV. In three of these patients (two on LEV monotherapy, one on LEV add-on to carbamazepine and phenobarbital) the new side effects were transient and disappeared spontaneously or after reduction of LEV oral doses, and did not lead to LEV withdrawal. The remaining patient reported persistent side effects (irritability) on LEV monotherapy: this problem, however, was better tolerated than previous adverse effects (dizziness on carbamazepine treatment) and did not lead to LEV withdrawal.

The 19 patients of the De Novo Group had never been treated with AEDs and LEV monotherapy was introduced as the first-line drug because of its favorable profile. Thirteen patients in this group had focal epilepsies while the remaining had generalized epilepsies. There were 17 patients out of 19 (89.5%) in this group that were responsive to LEV, in particular with 11 seizure-free (57.9%). One of the responding patients reported adverse effects (irritability) which did not lead to drop out from LEV treatment. The two patients (10.5%) who did not respond to LEV were switched to different AEDs after six months of LEV mono-therapy. In both of them seizures persisted on a polytherapy regimen.

The 122 patients of the Drug Resistant Group had long-standing drug resistant seizures which had failed to respond to at least two other prior AEDs appropriate for their epilepsy classification. Twelve of them had been gradually switched to LEV monotherapy from previous treatment, while the remaining 110 received LEV as add-on therapy. Sixty-four patients (52.5%) in the Drug Resistant Group were responsive to LEV, with 28 seizure-free (23.0%). Statistical analysis (Table 4) showed that a good outcome was significantly associated with LEV monotherapy, low LEV daily doses, fewer concomitant AEDs, and reversely associated with presence of abnormal MRI findings, history of surgery (or indication for surgery) for epilepsy, history of status epilepticus. No significant association with sex, age and epilepsy type were observed.

The Drug Resistant Group included 26 patients with IGE, 6 with SGE, 1 with IFE, 32 with CFE and 57 with SPE. Idiopathic generalized epilepsy patients showed the best response with 69.2% responsive patients (42.3% seizure-free), while in CFE 53.1% were responsive to LEV (25.0% seizure-free) and in SFE 47.4% were responsive to LEV (14.0% seizure-free). These differences, however, were not significant (Figure). The groups

of SGE and IFE patients were not included in the statistical analysis due to their small size; SGE had only one responsive patient (16.7%), who was not seizure-free, and the only patient belonging to the IFE group was seizure-free.

Conclusions

The aim of our study was to evaluate, retrospectively, efficacy and tolerability of LEV in patients who had received this drug in the setting of a clinical practice and had not been selected according to a specific study protocol. For this reason, our patient population was quite heterogeneous. Other limitations of our study were the retrospective evaluation of patients and the lack of LEV plasma levels in several patients, which did not allow a satisfactory evaluation and accurate conclusions on this specific issue.

While tolerability was evaluated in the group as a whole, subdivision in different groups allowed an evaluation of efficacy specifically oriented to different clinical features of patients.

In the first group (Controlled Seizures Group), whose patients were already seizure-free, the goal was to maintain seizure freedom while reducing or abating adverse effects related to previous AED treatment.

Because of its favorable pharmacokinetics and good tolerability, LEV is often employed as alternative treatment in patients whose seizures are already controlled with other AEDS, but in whom adverse effects related to treatment have a significant impact on quality of life. In our study, preservation of seizure freedom in these patients was observed in 96.8%, disappearance or relevant reduction of previous adverse effects in 100%, and onset of persistent, but well tolerated LEV-related adverse effects in 3.2%.

The second group (De Novo Group) included patients who had never been treated with AEDS. In newly diagnosed patients the choice of LEV as first-line treatment is usually suggested in special populations such as elderly patients, liver impaired subjects or patients submitted to poly-treatment for co-morbidity. However, due to its efficacy on different kinds of seizures together with good tolerability and favorable pharmacokinetic profile, LEV is gradually becoming a first-choice option in wider populations of epileptic patients. In our study, 89.5% of newly diagnosed patients were responsive to LEV monotherapy, with 57.9% seizure-free.

The third group included patients with uncontrolled seizures (Drug Resistant Group). Drug Resistant patients are a population who present with a history of poor response to AED treatment and usually receive at least two different AEDs. In these subjects, LEV is usually employed as add-on treatment with the aim of controlling seizures; only successively, if seizure control is achieved, concomitant AEDs are reduced in number and dosage, and finally a switch to monotherapy is attempted. In our population of Drug Resistant subjects, 52.5% were responsive to LEV, with 23.0% achieving seizure freedom. Predictably, best results were observed in idiopathic epilepsies. As reported in other studies on refractory seizures[4], patients who responded best

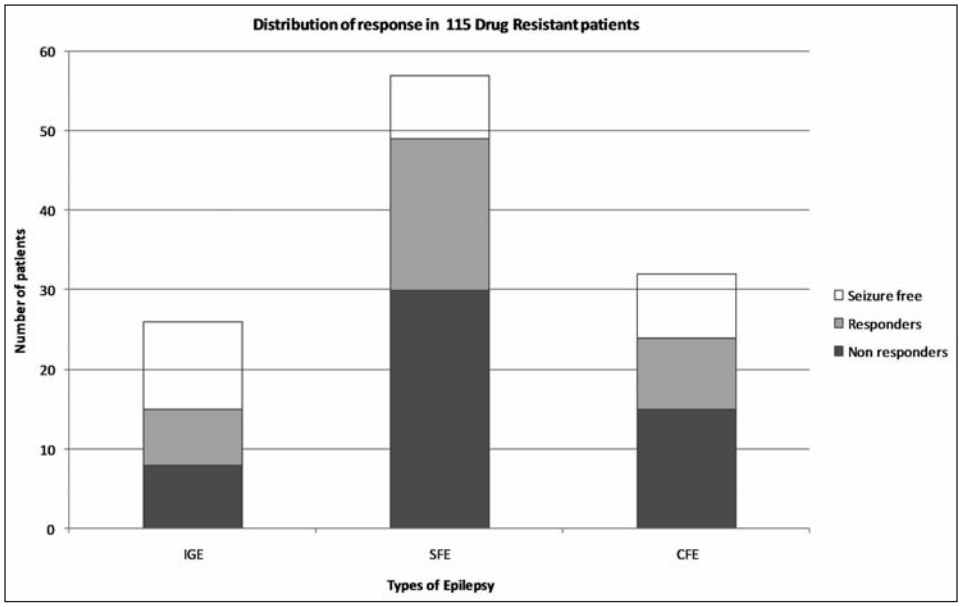

Figure: *Distribution of Drug Resistant patients with IGE (Idiopathic Generalized Epilepsy), SFE (Symptomatic Focal Epilepsy) and CFE (Cryptogenic Focal Epilepsy) with regard to response to LEV treatment. Seizure-free: reduction of 100% of seizures after LEV treatment. Responders: reduction of seizures > 50% but < 100% after LEV treatment. Non-responders: reduction of seizures ≤ 50% or seizures unchanged or seizures worsened after LEV treatment. No statistically significant differences were observed among the groups (chi-square).*

Table 4: Efficacy analysis (logistic regression) in 122 drug resistant patients

Univariate analyses			
Efficacy and age groups	**Odds ratio**	**P value**	**[95% Conf. Interval]**
25-39 vs < 25	.7169761	0.519	.2608699 1.97054
40-54 vs <25	1	1.000	.3523691 2.837933
55+ vs < 25	1.452369	0.538	.4424346 4.767657
Efficacy and sex	**Odds Ratio**	**P value**	**[95% Conf. Interval]**
Males vs Females	1.773318	0.095	.9060325 3.4708
Efficacy and Epilepsy Type	**Odds Ratio**	**P value**	**[95% Conf. Interval]**
Focal vs Generalized	1.738373	0.156	.8099748 3.730906
Efficacy and LEV Monotherapy	**Odds ratio**	**P value**	**[95% Conf. Interval]**
Monotherapy vs Polytherapy	20.14714	0.000*	4.055581 100.0861
Efficacy and MRI findings	**Odds Ratio**	**P value**	**[95% Conf. Interval]**
Abnormal MRI vs normal MRI	.4252744	0.014 *	.2154707 .8393636
Efficacy and Surgery for epilepsy	**Odds Ratio**	**P value**	**[95% Conf. Interval]**
Surgery vs no Surgery	.276395	0.020*	.09382 .8142637
Efficacy and Status	**Odds Ratio**	**P value**	**[95% Conf. Interval]**
Status vs no Status	.3493075	0.007 *	.1635491 .7460497
Efficacy and Adverse Effects to LEV	**Odds ratio**	**P value**	**[95% Conf. Interval]**
Adverse effects vs no adverse effects	1.353073	0.551	.5009527 3.654652
Efficacy and # of concomitant AEDs	**Odds ratio**	**P value**	**[95% Conf. Interval]**
# of concomitant AEDs	.251247	0.000 *	.1494734 .4223163
Efficacy and LEV daily dose	**Odds ratio**	**P value**	**[95% Conf. Interval]**
Daily LEV dose	.580947	0.002 *	.4127212 .8177419
Efficacy and LEV plasma levels	**Odds ratio**	**P value**	**[95% Conf. Interval]**
LEV plasma levels	1.04043	0.074	.9962196 1.086603
Multivariate analyses			
1. **Analysis of age, sex, and LEV daily dose**			
	Odds ratio	**P value**	**[95% Conf. Interval]**
25-39 vs < 25	.8230166	0.711	.293895 2.304756
40-54 vs < 25	1.258741	0.674	.4313118 3.673512
55 + vs < 25	1.192494	0.777	.3526369 4.032594
Males vs Females	1.981465	0.054	.9896566 3.967238
Daily LEV dose	.5627576	0.002*	.3922512 .807381
2. **Analysis of age, sex, and all significant univariate predictors (except LEV plasma levels)**			
	Odds ratio	**P value**	**[95% Conf. Interval]**
25-44 vs < 25	1.235113	0.718	.3922582 3.889032
45-55 vs < 25	1.649547	0.418	.4911258 5.540345
55 + vs < 25	.9867958	0.984	.2603021 3.740907
Males vs Females	1.493099	0.299	.7003339 3.183261
Monotherapy vs Polytherapy	2.686616	0.303	.4091033 17.64323
Abnormal MRI vs normal MRI	.7360832	0.456	.3286816 1.64846
Surgery vs no Surgery	.4495551	0.212	.1281862 1.576612
Status vs no Status	1.132368	0.796	.4403275 2.912055
# of concomitant AEDs	.3480213	0.002 *	.1799145 .6732023
Daily LEV dose	.6218403	0.017 *	.421503 .9173964
3. **Analysis of age, sex, and all significant univariate predictors (except LEV plasma levels, LEV daily dose, and number of concomitant drugs)**			
	Odds ratio	**P value**	**[95% Conf. Interval]**
25-44 vs < 25	.9077493	0.855	.3211944 2.565452
45-55 vs < 25	1.332176	0.610	.4425685 4.009988
55 + vs < 25	1.440662	0.555	.4289258 4.838848
Males vs Females	1.725656	0.125	.8600213 3.462574
Abnormal MRI vs normal MRI	.6018241	0.193	.2801784 1.29272
Surgery vs no Surgery	.4192681	0.149	.128808 1.364711
Status vs no Status	.5110502	0.149	.2221899 1.175446
4. **Analysis of all predictors (except LEV plasma levels)**			
	Odds ratio	**P value**	**[95% Conf. Interval]**
25-44 vs < 25	1.190335	0.767	.3760721 3.767623
45-55 vs < 25	1.631631	0.433	.4794847 5.552254
55 + vs < 25	.9549959	0.947	.2468104 3.695214
Males vs Females	1.541185	0.269	.716217 3.316384
Focal vs Generalized	1.03636	0.944	.3795099 2.830077
Monotherapy vs Polytherapy	2.780445	0.289	.4199812 18.40766
Abnormal MRI vs normal MRI	.7913488	0.599	.3308041 1.893062
Surgery vs no Surgery	.418945	0.186	.11525 1.522906
Status vs no Status	1.138466	0.792	.4348458 2.980609
Adverse effect vs no adverse effects	1.580736	0.484	.4390196 5.691606
# of concomitant AEDs	.339599	0.001 *	.1745665 .6606507
Daily LEV dose	.6493361	0.036 *	.4333112 .973059
5. **Analysis of all predictors (except LEV plasma levels, LEV daily dose and number of concomitant drugs)**			
	Odds ratio	**P value**	**[95% Conf. Interval]**
25-44 vs < 25	.9051249	0.851	.3191666 2.566844
45-55 vs < 25	1.406364	0.547	.4633618 4.2685
55+ vs < 25	1.484623	0.529	.4341604 5.076707
Males vs Females	1.843787	0.091	.906636 3.749629
Focal vs Generalized	1.448921	0.428	.5797286 3.621304
Abnormal MRI vs normal MRI	.7130769	0.421	.3128326 1.625402
Surgery vs no Surgery	.4281612	0.170	.1274486 1.4384
Status vs no Status	.474744	0.086	.2028991 1.110807
Adverse effects vs no adverse effects	1.379115	0.581	.4401226 4.321428

• Statistically significant

tended to do so at relatively low doses; good outcomes were predictably associated with fewer concomitant AEDs and more frequent switch to monotherapy. Our study did not allow identification of a specific profile of Drug Resistant patients who could be predicted to be responsive to LEV. The only potentially useful suggestion is that "markers" of severe epilepsy (MRI abnormal findings, history of status, past or programmed surgery for epilepsy) are quite obviously associated with a poor outcome. Outcome does not significantly change in relation to sex, age or epilepsy type (if focal or generalized), and while Idiopathic Epilepsies tend to show a better response than Cryptogenic and Symptomatic forms, the difference among the groups is not significant.

Tolerability to LEV was evaluated in the whole group of 202 patients. Adverse reactions to LEV were significantly associated with low oral doses and low plasma levels, suggesting that patients likely to develop adverse effects tend to show them quite early during LEV treatment and that adverse effects are not related to high dosages. There was no significant association of adverse effects with polytherapy, suggesting that impaired tolerance to LEV might not be related to interactions with concomitant AEDs.

Finally, there was a significant predominance of female patients in the group of subjects with adverse effects: this finding, which might suggest a difference in tolerability related to gender, is at the moment quite difficult to interpret. So far, studies investigating tolerability of LEV have not shown differences relating to gender[10,11]. In our sample, no specific side effect was represented more in the female group, suggesting a global reduction of tolerability in women rather than a particular susceptibility to a specific adverse effect; this was also suggested by the fact that nearly 30% of women with adverse effects complained of more than one adverse effect, while this was never observed in male patients. Drop outs due to adverse effects were observed more often in women, but not significantly. There was no significant difference between males and females with regard to age, co-treatment and epilepsy type; within the female group adverse effects were equally distributed according to age, suggesting that impaired tolerability in these women was not related to a specific period of reproductive age. Further investigations in larger samples are warranted to confirm this interesting finding.

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