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Add-on Levetiracetam in Children With Refractory Epilepsy: A Systematic Review

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Abstract

Context: Recently, new anti-epileptic drugs are marketed to be used as an add-on to the traditional drugs in children with refractory epilepsy. Levetiracetam is a second-generation of new anti-epileptic drugs with unknown precise mechanism of action in brain and synaptic vesicle in children with drug resistant epilepsy. Herein, the efficacy and safety of add-on levetiracetam in children with refractory epilepsy is reviewed.

Evidence Acquisition: A literature review was performed on efficacy and safety of add-on Levetiracetam in children with refractory epilepsy using international databases with the following terms: levetiracetam, refractory epilepsy, drug resistant epilepsy, seizures/epilepsy, children/pediatric. All articles related to add-on levetiracetam in children with refractory epilepsy written in English and published from 2000 to 2015 were included. The title and abstracts of 542 articles were assessed, of which, 488 were excluded. The full texts of the other 54 articles were assessed for relevance.

Results: Of the nine eligible articles, 1036 patients aged $\leq$ 18 years were identified. Male patients (52%) were more prominent than female ones. Five articles reported that levetiracetam therapy appeared more effective against localization-related than generalized epilepsy. The dosage of levetiracetam ranged from 6 to 70 mg/kg/day, with a mean of 43.2 mg/kg/day based on the mean doses reported by four of nine reviewed articles. The mean duration of follow-up was 39 weeks (ranging from 8 - 144 weeks). Administration of levetiracetam was effective in 42.24% of the patients (responders with >50% decrease in seizure frequency), of whom 11.8% had become seizure free. The mean number of anti-epileptic drugs tried before introducing levetiracetam treatment was 4.4 (ranging 1 - 20). The most frequent side effects were psychological and behavioral changes (11.1%), followed by agitation (9.2%) and sleep disturbances (6.7%).

Conclusions: The current review demonstrated that levetiracetam, as an add-on therapy, is an effective and well-tolerated anti-epileptic drug, associated with reversible and no serious side effects, to control seizure frequency of childhood refractory epilepsy.

Keywords: Levetiracetam, Epilepsy, New Antiepileptic Drug, Childhood Refractory Epilepsy

1. Context

Over the past 15 years, a large number of new antiepileptic drugs (AEDs) are marketed and introduced to treat different types of seizures and epilepsy syndromes. Levetiracetam (LEV) is a second-generation antiepileptic drug approved as adjunctive therapy to treat partial onset seizures in adults since 2000 and in children with refractory epilepsy (1, 2).

Although the exact mechanism of action is still unknown, it was suggested that LEV might modulate SV2 protein interactions. Consequently, normal levels of SV2 and synaptotagmin at the synapse are maintained, which may lead to reduce seizures (1, 3). Also, it is suggested that LEV partially inhibits N-type high-voltage-activated Ca^{2+} currents and reduces the release of Ca^{2+} from intraneuronal stores (4-9). LEV has a favorable pharmacokinetic profile. It is well tolerated, safe and efficacious in several phase-III LEV studies of adult patients. LEV is almost completely absorbed after oral administration. It has low-protein binding fewer than 10%, no significant drug interactions and its bioavailability is approximately 100%. Levetiracetam metabolizes minimally and does not undergo hepatic metabolism. Renal excretion is the major elimination route for levetiracetam (1, 2, 10). The pharmacokinetics profile of LEV in children was similar to that of observed in adults, although clearance is approximately 30% - 40% higher, which is because of generally higher drug clearance among children compared with adults.

Several trials about add-on LEV in children and adolescents with refractory epilepsy showed the efficacy of LEV

both in partial and generalized seizures. Moreover, LEV administration in children was associated with low discontinuation rates due to adverse effects. The most common reported adverse effects were mild and reversible (2, 11-15).

Although previous trials demonstrated the efficacy of LEV both in adults and children, safety and efficacy of LEV in infancy remains ascertained. Therefore, there is still a critical need to review the literature and to identify the safety and efficacy of LEV as add-on or monotherapy in all age groups among children. Herein, the current evidence regarding efficacy and safety of add-on LEV in childhood refractory epilepsy is reviewed.

2. Evidence Acquisition

A literature review was performed on efficacy and safety of add-on levetiracetam used in children with refractory epilepsy on PubMed in Medline area, Google Scholar, Embase, Ovid, ProQuest and Cochrane databases with the following terms: levetiracetam, keppra, refractory epilepsy, drug resistant epilepsy, seizures/epilepsy, children/ pediatric. All articles related to add-on levetiracetam in children with refractory epilepsy written in English and published from 2000 to 2015 were included. Articles not related to children, other anti-epileptic drugs, not add-on, duplicates and abstracts of congress proceedings were excluded. The title and abstracts of 542 articles were assessed, of which, 488 were excluded. From the 54 remained relevant articles, nine were included for review. The reference lists of these publications were also searched for more articles relevant to the topic. Data were independently extracted from the articles by SSH and controlled by AA. Although the two authors evaluated the study designs and possibility of any risks of bias in the selected studies, publication bias may, however, have led to an unrealistic positive view of the efficacy and safety of levetiracetam.

3. Results

As shown in Figure 1, after removing duplicates, evaluating titles and abstracts, removing articles not related to the children, nine articles were included in the review: two retrospective studies, five prospective open-label studies and 2 randomized controlled trial.

Summary of data derived from the nine reviewed articles is shown in Table 1. A total of 1036 patients aged $\leq$ 18 years (mean 5.8 years) were identified, 472 (46%) were female, 544 (52%) were male and 20 (2%) were not identified because of lack of data. Involvement of male patients was more prominent than female ones in all the reviewed articles. The most common diagnosis was focal epilepsy syndrome (72%) followed by general epilepsy syndrome (14.2%), unclassified (4.7%), Lennox Gastaut syndrome (1.45%) and 7.6% were the other types of epilepsy. The most common cause of epilepsy syndrome was symptomatic (58.9%) followed by cryptogenic in 26.8% and idiopathic in 10.3%. From the nine reviewed articles, five reported LEV therapies appeared more effective against localization-related than generalized epilepsy. The dosage of LEV ranged from 6 to 70 mg/kg/day, with a mean of 43.2 mg/kg/day based on the mean doses reported by four of the nine reviewed articles. The mean duration of follow-up was 39 weeks (ranged from 8 to 144 weeks). Administration of LEV was effective in 42.24% of the patients (responders with $>$ 50% decrease in seizure frequency), of whom 11.8% had become seizure free. In 23.3% of the patients, LEV had minimal seizure reduction (responders with $\leq$ 50% decrease in seizure frequency). No change (defined as seizure reduction $<$ 20%) was reported in 7.6% of the patients. Increase of seizure frequency $\geq$ 50% was reported in 5.2% of the patients. The retention rate for responders was reported by four of the reviewed articles. The maximum and minimum retention rates were 19% and 70% after 48 and 26 weeks follow-up, respectively. The rate of adverse events was 51.1%. Except two patients (0.2%) with hemorrhagic colitis and apnea, there were no other adverse events. The most frequent side effects were psychological and behavioral changes (11.1%), followed by agitation (9.2%), sleep disturbances (6.7%), gastrointestinal disturbances (6.7%) and fatigue (5.9%). It was reported that the antiepileptic drugs (AEDs) administered at onset of LEV therapy included valproate (43.01%), phenobarbital (21.75%), carbamazepine (25.55%), vigabatrin (17.76%), topiramate (24.65%), lamotrigine (16.05%), adrenocorticotropic hormone (ACTH) (10%), benzodiazepines (24.73%) [included: clonazepam (13.9%), chlormethyldiazepam (8%) and others (52.3%)], gabapentin (9.5%), tiagabine (9.52%), phenytoin (6.25%), clobazam (15.16%), ethosuximide (9.1%). As reported by six of the nine reviewed article, the mean number of AEDs tried before introducing LEV treatment was 4.4 (ranging 1 - 20).

4. Discussion

Drug-resistant epilepsy is an evident in 20% - 30% of patients with seizure disorders and still remains a challenge in clinical pediatric neurology. In recent years, a number of new antiepileptic drugs (AEDs) are introduced as an add-on to the clinical practice to improve seizure control in pediatric patients. Levetiracetam (LEV) is one of the new AEDs representing useful drugs in children with drug-resistant epilepsy (2, 16, 17).

The current review indicated that LEV, as an add-on AED, was effective and well-tolerated in 42.24% of the pe-

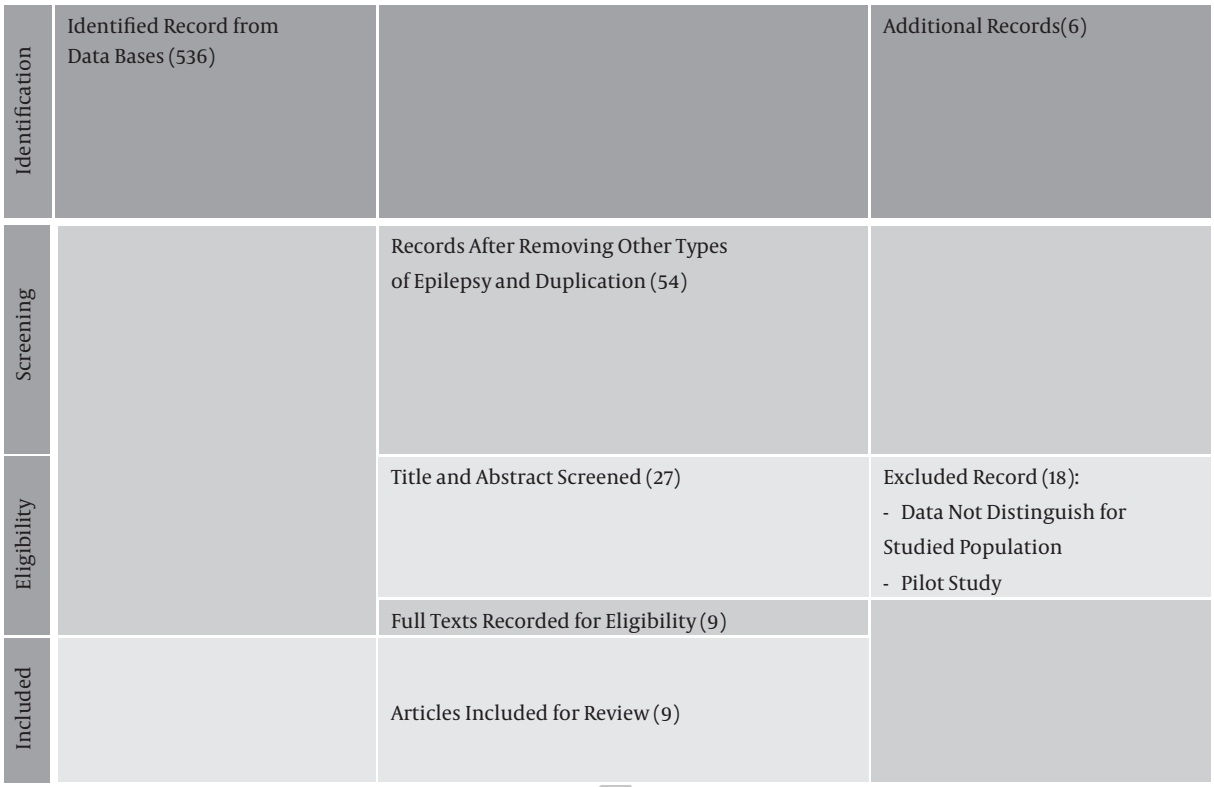

Figure 1. The Flow Diagram of Study Selection

diatric patients ≤ 18 years with refractory epilepsy to reduce more than 50% of seizure frequencies, of whom 11.8% had become seizure free. Similar findings were observed by others (13, 18). Opp et al. reported 24.9% of the responders with more than 50% of seizure reduction during LEV therapy that was less than the current review results (2). They explained that the cause of lower responder rate was patients with highly refractory epilepsies that investigated in their study and treated with a high number of AEDs before LEV was added on (mean: 7 AED), and a long duration of epilepsy (mean: 6.0 years) compared to the age of the patients (9.9 years) and the presence of frequent mental retardation (92.1%). In the study by Callenbach et al., more than 50% of the children had a seizure reduction of more than 50% after 26 weeks of LEV therapy, and 27% were seizure free for at least 4 weeks at the end of the study that was higher than the results of the current review (10). Kanemura et al. reported the response rate of 54.1% (16). Grosso et al. reported that levetiracetam administration was effective (responders with > 50% decrease in seizure frequency) in 39% of children, of whom 10 (9%) became seizure-free (11). The study by Lagae et al. showed seizure frequency reduction of more than 50% in 47% of children very early after introducing the LEV. They concluded that it can indicate successful treatment with LEV in partial and generalized seizures, with a significant effect on myoclonic seizures (12). In the study by Stuelpnagel et al. (17) the rate of responders was 27.1% that was lower than those of other long-term studies (58.1%, 55% and 53.1%) (13, 19, 20). They explained this difference by the highly refractory patient population and the strict definition of responders (seizure reduction of more than 50% and after 6 months of LEV therapy) (17). In another study by Grosso et al. in 2007, on children less than four years with refractory epilepsy, 30% of the patients had more than a 50% seizure reduction. They concluded that the lower response rates they observed might be because of insufficient experience with LEV in young children, resulting in a very strong selection bias for infants with highly refractory epilepsies (15). On the contrary, Pina-garza et al. reported that adjunctive levetiracetam was an effective and well-tolerated treatment for partial-onset seizures inadequately controlled with one or two antiepileptic drugs in children aged one month to less than four years (18).

The current review found that in most of the reviewed articles, LEV efficacy was evaluated in relation to epilepsy syndromes rather than to seizure types. Four of the nine reviewed articles reported that LEV therapy appeared more effective against partial seizures than against generalized seizures (2, 10, 13, 16). Opp et al., showed no significant differences in the responder rates dependent on epilepsy syndromes, but they found that the responder rates differed between seizure types. Focal seizures responded better than generalized seizures. These results were similar to the results reported by Wheless and Ng (21). Callenbach et al. reported that LEV was effective in both partial and generalized seizures, but was more effective in partial seizures (10). On the contrary, Stuelpnagel et al. reported equal efficacy of LEV in the treatment of focal and generalized seizures, even though the ones patients with generalized epilepsy had better responses to the treatment of LEV than patients with partial epilepsy (17).

The results of the current review showed that the dosage of levetiracetam ranged from 6 to 70 mg/kg/day, with a mean of 43.2 mg/kg/day based on the mean doses reported by four of the nine reviewed articles (2, 10, 15, 16). Opp et al. reported that in the 13 patients who became seizure free, the mean dosage of LEV was 35.8 $\pm$ 20.6 mg/kg/day. They suggested that most treatable patients respond in the 30 - 40 mg/kg/day range (2). In a cohort study by Callenbach et al., the mean dosage of LEV at the end of the trial was 26.5mg/kg/day (10). It was lower than the mean dosage of 37 - 53 mg/kg/day reported by the others (2, 14-16, 21, 22). Their explanation for the lower daily dosage of LEV was being more careful than their investigator in up titrating to find a good balance between tolerability and efficacy. The higher LEV dosage (53.3mg/kg/day) was prescribed by Wheless and Ng, that the effect was most pronounced in partial seizures (21). Kanemura et al. reported that some of the seizure-free patients showed a bipolarization tendency with a lower dosage of 19.4 mg/kg/day and with higher dosage of 59.1 mg/kg/day. They suggested that the appropriate dosage of LEV is different individually and LEV may decrease seizure frequency in a dose dependent manner in some patients (16). Side effects were reported to be more frequent with LEV dosage higher than 40 mg/kg/day (12). However, a report emphasized that LEV was tolerated at the dosage of 270 mg/kg/ day (23). It can be concluded that the higher side effects found in the current review may be due to the mean dosage of LEV that was higher than 40 mg/kg/day.

The mean duration of follow-up in the current review was 39 weeks (range from 8 - 144 weeks). Grosso et al. (15) and Peake et al. (14) found a decrease in the number of patients being seizure free during follow-up. Grosso et al. reported that 31% of their patients after three months and 15% after 12 months were seizure free (15). Peake et al. reported 14% seizure free patients after two and six months and 5% after 12 months (14). According to the results of these studies, it can be concluded that duration of follow-up is influenced by the percentage of patients being seizure free.

The retention rate is defined as an important measure of the overall drug effectiveness because it represents a reliable combination measurement of adverse events and efficacy over time (24). The retention rate for responders was reported by four of the nine reviewed articles. The maximum and minimum retention rate was 19% and 70% after 48 and 26weeks follow-up, respectively (10, 15). Opp et al. and Stuelpnagel et al. reported the retention rates of 33.5% after 12 weeks and 22.5% after 144 weeks, respectively (2, 17). It was suggested that retention rate inversely correlated with the duration of follow-up and the kind of patients included in the study (10, 17).

Although the adverse events identified in this review were quite frequent (51.1%), except two patients (0.2%) with hemorrhagic colitis and apnea, others were reversible and not serious side effects that could be limited by titration period and seldom by withdrawal of the drug (2, 10-13, 15-18). In the present review, the most frequently adverse effects were similar to the ones reported by others including psychological and behavioral changes (11.1%), agitation (9.2%) and sleep disturbances, specially somnolence in 6.7% of the patients (2, 10-12, 25-27). It is reported that side effects occur mainly in LEV dosages higher than 40 mg/kg/day (11-13, 15, 17, 18, 25-27). Somnolence was the most common side effect reported by Opp et al. and caused discontinuation of LEV in three patients. They believed that mental retardation and physical handicap among their studied population played a role as a risk factor for experiencing somnolence during LEV treatment (2). It was the most common side effect reported by the seven of the reviewed articles (2, 10, 11) Behavioral and emotional changes were also reported as the most common cause of withdrawal of LEV (2, 11, 17, 28). Younger patients were reported to be more susceptible to side effects, specially behavioral and emotional changes compared to the large phase III studies in adults (19, 29, 30).

The most common anti-epileptic drugs (AEDs) reported to be administered at the start of LEV therapy were valproate (43.01%), carbamazepine (25.55%), benzodiazepines 24.73%, topiramate (24.65%), and phenobarbital (21.75%). As reported by six of the nine reviewed articles, the mean number of AEDs tried before introducing LEV treatment was 4.4 (ranging 1 - 20). The idiosyncratic seizure activation by LEV was reported by Opp et al. in 10% of their patients. This phenomenon is also reported by others (31, 32).

4.1. Conclusion

In conclusion, the current review supports the available data to date that LEV is an effective, safe and well tolerated anti-epileptic drug as a valid therapeutic option in infants and young children with refractory epilepsy because of its favorable tolerance profile, the option of fast titration and the seldom drug interactions. Monitoring of the side effects in pediatric patients with additional comorbidities is recommended.

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Table 1. Summary of Data Extracted From the Nine Reviewed Articles on Efficacy and Safety of Levetiracetam in Children With Refractory Epilepsy

Author/Date	Study Design	Dx.	No. of Patients/Gender	Age (y/o)	Dosage (mg/kg/day)	Follow-up, Months	Efficacy (%)	Retention Rate	Adverse Effect (%)/ No. (%)	AEDs Before LEV/after LEV, No. (%)
(15) **Grosso et al., 2007**	Retrospective	Focal epilepsy (30): - Probably symptomatic (12); - Symptomatic (18); West syndrome (17): - Cryptogenic (7); - Symptomatic (10); Lennox-Gastaut (2); Myoclonic-astatic(2); Eyelid myoclonia (2); Dravet syndrome (3); Early myoclonic Encephalopathy (6); Unclassifiable (19)	81 F = 36; M = 45	< 4 y Mean = 27 m (2 - 46 m)	5 - 10 mg/kg/bid, ↑ weeky 62 mg/kg/day, Mean LEV Daily dose = 41 mg/kg (25 - 62 mg/kg/day)	9	SF = 10 (12%) ↓> 50% = 14 (30%) ↓21%-50%= 18 (22%), ↓<20 (unchanged) = 24 (30%), ↑> 50% comparison baseline = 15 (18%)	After 12 months follow-up: 9 (19%)	Drowsiness (45%), Nervousness (36%) Cognitive disturbances (29%) Loss of appetite (14%), Sleep disturbances (7%), Vomiting (4%)	Mean = 4 (1-10)/ mean = 2 (1-3); [Valproate (41%), Phenobarbital (31%), Carbamazepine (27%) Vigabatrin (26%) Topiramate (22%), Clonazepam (20%) Lamotrigine (9%), Oxcarbazepine (7%) Chlormethyldiazepam (6%) ACTH (10%)]
(2) **Oppet al., 2005**	Retrospective	Epilepsy syndrome: -Focal 191 (67.0%); -Generalized 49 (17.2%); -Focal and generalized signs 45 (15.8%)	285, F = 128, M = 137, ND = 20	Mean: 9.9 y Ranging: 0-17	Maximum dose 47.7±21.8 mg/kg/day	≥ 12	SF = 13 (6.2%), ↓≥ 50% = 39 (18.7%), ↓< 50% no significant change = 136 (65.1%), Increase of >100% = 14 (6.7%), Not evaluated = 7 (3.3%)	70 (33.5%) of the 209 patients at the last visi	- Somnolence/fatigue 52 (18.2), -Somnolence only initially 16 (5.6), -Sleeping disturbance 9 (3.1), -Behavioral changes 44 (15.4): Aggression 30 (10.5), Altered mood 8 (2.8), - Loss of appetite 10 (3.5), -Vomiting 6 (2.1), -Tremor 6 (2.1), -Cognitive disturbance 5 (1.8), - Severe side effects: - Hemorrhagic colitis 1 (0.4), - Apneas 1 (0.4)	6.8 (ranging 0 - 20) AED on average and only 31 patients (11.0%), The most prevalent co-medication was valproic acid (VPA) in 133 patients (47.7%), followed by lamotrigine in 44 patients (15.8%) and oxcarbazepine in 43 patients (15.4%)
(12) **Lagae et al., 2003**	Open-label add-on trial	- Partial and generalized seizures -Lennox Gastaut syndrome = 5pts, Identifiable lesions on MRI = 8 pts-Mild or severe mental retardation = all 21 pts	21, F = 11, M = 10	11 months and 14 years, old, (mean age = 5y)	10 mg/kg/day, increased every 4th day by 10 mg/kg up to a maximum of 60 mg/kg/day	12 w	SF = 1 (4.76%), ↓> 50% = 10 (47%), ↓< 10% (unchanged) = 8 (38.1)	no data	-Headache = 1, -Increased somnolence = 2, -Behavioral changes = 1, - Incr. alertness = 4	- Valproic acid, - Vigabatrine, - Lamotrigine, - Benzodiazepine, -Topiramate, -Gabapentin, -Carbamazepine, -Tiagabine , -Phenobarbital-phenytoin
(17) **Stuelpnagel, 2007**	Prospective add-on trial	- Different severe epilepsy syndromes, - Focal epilepsy 79 (61.2%): Symptomatic 64 (81%), Cryptogenic 15 (19%), - Generalized epilepsy 36 (27.9%): symptomatic 19(52.8%), Cryptogenic 9 (25%), Idiopathic 8 (22.2%), -Unclassified epilepsy 14 (10.9%)	129, F = 46, M = 83	(Mean age=10.6y) 6 m-39 ys 9 ms	Maximum LEV dosage was 39.8 mg/kg/day (ranging 6-70 mg/kg/day)	3 y in 35 responders pts	SF = 5(3. 9%), ↓≥ 50% = 35(27.1%) ↓< 50% = 8, - ↑seizure = 1	29 (22.5%); after 3 years follow-up	The rate of side effects = 39.8%, The most common side effects: -Fatigue (12.5%); -Aggressiveness (7.8%), -Gastrointestinal disorders (13.3%)	-Valproic acid= 57 (44.2%), -Oxcarbazepine= 29 (22.5%), -Clobazam =24 (18.6%), -Lamotrigine= 20 (15.5%), -Other= 75 (58.1%)
(10) **Callenbach et al., 2008**	Prospective multi-center, open-label, add-on	-Seizure type (%), -Simple partial seizures, 2 (6.1), -Complex partial seizures, 19 (57.6), -Partial onset with secondary generalization 10 (30.3), -Generalized tonic-clonic, 2 (6.1) -Tonic 4 (12.1), -Atonic 1 (3.0), -Clonic 0, -Myoclonic 4 (12.1), -Absences 6 (18.2), -Unclassified seizures 1 (3.0); -Epilepsy syndrome No. (%): Symptomatic localization-related epilepsy not further defined 11 (33.3). Cryptogenic localization-related epilepsy 8 (24.2) Juvenile absence epilepsy 1 (3.0); Idiopathic generalized epilepsy not further defined. 2 (6.1)Epilepsy with myoclonic-astatic seizures 1 (3.0), Symptomatic generalized epilepsy not further, defined 8 (24.2); Epilepsy undetermined whether focal or generalized 1 (3.0), Not known 1 (3.0)	33, F = 16 (48.5); M = 17 (51.5)	4 - 16 y	10 mg/kg/day was increased with 2 week up to a maximum dose of 60 mg/kg/day	26 w	SF = 9(27%), ↓> 50% = 17 (51.5%), Unchanged = 4, ↑seizure = 4	23 (69.7%) after 26 weeks	Most common complaints were hyperactivity, (48.5%), somnolence (36.4%), irritability (33.3%) and aggressive behavior (27.3%)	Valproic acid (45.5%), lamotrigine (33.3%), carbamazepine, (27.3%), oxcarbazepine (15.2%), clobazam (15.2%), ethosuxi-mide (9.1%), topiramate (9.1%), clonazepam (6.1%), and phenytoin (3.0%)
(18) **Pina-Garza et al., 2009**	Multicenter, double-blind, randomized, placebo-controlled study	Refractory partial-onset seizures	111 patients (58, 96.7% Levetiracetam; 53, 94.6% placebo)	From 1 m to < 4 years	In patients aged 1 to < 6 months, levetiracetam was initiated at 20 mg/kg/day and titrated to 40 mg/kg/day; in patients aged 6 months to <4 years, levetiracetam was initiated at 25 mg/kg/day and titrated to 50 mg/kg/day	Long term follow-up	↓ ≥50%: in LEV group=25(43.1%) vs.in placebo = 10 (19.6%,)	No data	Adverse event, levetiracetam,/placebo no. (%), Somnolence 8 (13.3) / 1 (1.8), Irritability 7 (11.7)/ 0, Pyrexia 3 (5.0) /4 (7.1), Constipation 2 (3.3)/ 3 (5.4), Vomiting 2 (3.3)/ 3 (5.4), Insomnia 1 (1.7) /3 (5.4), Rash 1 (1.7)/ 3 (5.4)	Levetiracetam/placebo, No. (%): Valproic acid 25 (41.7)/21 (37.5) Phenobarbital 22 (36.7)/18 (32.1), Topiramate 21 (35.0) /16 (28.6), Oxcarbazepine 14 (23.3)/ 8 (14.3), Vigabatrin 8 (13.3)/ 11 (19.6), Clobazam 7 (11.7) / 3 (5.4), Carbamazepine 5 (8.3)/ 13 (23.2), Clonazepam 3 (5.0) / 9 (16.1)

(11) **Grosso et al, 2005**	Multi-centric, prospective and uncontrolled study	Epilepsy syndromes: -localization related epilepsy (53): cryptogenic(22), symptomatic(31);- generalized(45): myoclonic-astatic epilepsy (6); The Dravet syndrome (6); cryptogenic generalized (4); infantile spasms (5); Ohtahara syndrome (2) NR; Lennox-Gastaut (8) startle epilepsy (3) symptomatic generalized (11) - unclassifiable(12)	110 children, (52 females and 60 males)	< 16 y, mean = 7.7 y (ranging 6 m-15.9 y)	10 - 60 mg/kg/day (median 38 4.1)	2 - 20 months (median 7.6)	SF = 10(9%), ↓≥ 50%= 43 (39%), ↓< 50%= 27, ↓< 20% unchanged = 28 (25%), ↑≥ 50% = 12 (11%)	-	- The main side effects of somnolence and irritability occurred in 16 (14%) of patients	- The number of AEDs, administered at onset of LEV treatment ranged, from one to five (median two): - Valproate (46%) - Carbamazepine (37%) - Vigabatrin (27%), - Topiramate (26.5%), - Clonazepam, (24.5%), -Lamotrigine (18.5%), -Chlormethyldiazepam, (9%) -Phenobarbital (5%)
(16) **Kanemura, 2013**	Prospective	-Epilepsy symptomatic/cryptogenic (54); - Idiopathic (7); -Generalized epilepsy (7); -Localization related epilepsy (48); -Undetermined epilepsy (3); -Unclassified epilepsy (3)	61, F= 25; M = 36	16 m - 18 y (mean= 5.9 y)	10 mg/kg/ day up to a maximum of 60 mg/kg/day according to the participants' clinical seizures	At least 6 months of follow-up	SF in epileptic syndrome =15 (24.6%): -Localization-related epilepsy = 12, -Generalized epilepsy = 1; -Undetermined = 2; Responder = 33; (51.4%): -Localization related epilepsy = 28, -Generalized epilepsy = 3, -Undetermined, =1, 25- < 50% minimal response = 17, Unchanged = 3	-	-Drowsiness: 2 pts (3.3%)	Mean number of AEDs tried, before LEV = 5.2 (ranging 2 – 8) -Number of concomitant medications at the time of LEV (1 - 3, mean = 2.3)
(13) **Glauser et al., 2006**	RCT	Drug-resistant partial-onset seizures	198 (LEV = 101, placebo = 97), F ≈ 98, M ≈ 100	4 - 16 y	Target dose of 60 mg/kg/day	14w	SF = 7 (6.9%) patients who received leveti racetam and one patient (1.0%) who received placebo, ↓≥ 50% = 45(44.6%), in LEV group vs 19(19.6%) in placebo group	-	Specific adverse event (LEV/placebo), Somnolence 23/11, Accidental injury 17/10, Vomiting 15/ 13 Anorexia 13/ 8, Rhinitis 13/ 8, Hostility 12/ 6, Cough increased 11/ 7, Pharyngitis 10/ 8, Nervousness 10/ 2, Asthenia 9/ 3, Diarrhea 8/ 7, Personality disorder 8/ 7, Dizziness 7/ 2, Emotional lability 6/ 4, Pain 6/ 3, Agitation 6/ 1	% Receiving concomitant AEDs, (in 10% of patients) carbamazepine 34.7 38.1, topiramate 28.7 32.0, valproate 25.7 28.9, lamotrigine 22.8 20.6, oxcarbazepine 12.9 10.3

Abbreviation: ACTH, adrenocorticotropic hormone; AEDs, anti-epileptic drugs; NR (Not reported); MRI, magnetic resonance imaging; RCT, randomized controlled trial.