Effectiveness and Tolerability of Treatment with Vimpat (Lacosamide) in Children: A Systematic Review

Hossein Farshadmoghadam[1], Pourandokht Gholami Shirazi[2*]

[1]*Assistant Professor of Pediatric Neurology, Department of Pediatrics, Children Growth Research Centre, Research Institute for Prevention of Non-Communicable Disease, Qazvin University of Medical Science, Qazvin, Iran.*

[2*]*Assistant Professor of Neonatology, Department of Pediatrics, Children Growth Research Centre, Research Institute for Prevention of Non-Communicable Disease, Qazvin University of Medical Science, Qazvin, Iran. E-mail: shirazipooran@yahoo.com*

Abstract: Epilepsy is the most usual neurological problem in children worldwide, and the longer the seizure lasts during epilepsy, the more difficult it is to terminate, and the greater the risk of developing it. One of the drugs used to treat this disease is Vimpat (lacosamide) which has low drug interaction; therefore, it is suitable for monotherapy and polytherapy (multidrug therapy) in children. The present study is a systematic review, conducted by searching the databases of Elsevier, PubMed, Springer, and Wiley and with the keywords of status epilepticus, children, lacosamide, seizures, efficacy, and tolerability; studies that were performed between 2011-2019 were reviewed. Out of a total of 763 articles, 17 articles were finally selected for further review, based on the inclusion and exclusion criteria. The results showed that the use of lacosamide was associated with improved physical conditions and reduced seizures in children and its therapeutic role in pediatrics was significant. However, to better understand the role of this drug and its safe and appropriate dose in children, it is necessary to conduct further studies in this field.

Keywords: Vimpat, Lacosamide, Children, Efficacy, and Tolerability.

1. INTRODUCTION

Epilepsy is the most common neurological problem in children worldwide. Its yearly prevalence is 20 people per 100,000 children. The rate of mortality from the disease is low, but factors such as disabilities and neurological disorders, learning disabilities, drug-resistant epilepsy, and de-novo epilepsy can increase the incidence and prevalence of epilepsy by up to 22%. The longer the seizure lasts during epilepsy, the more difficult it is to stop and terminate, and the greater the risk of developing it [1]. Seizures are the most usual cause of neurological counseling in the Pediatric Intensive Care Unit (PICU). With the growing use of continuous electroencephalography (EEG) monitoring in children with acute encephalopathy, electrographic seizure activity is mostly identified, and whereas this seizure is associated with adverse neurobehavioral outcomes, most physicians use anticonvulsant drugs to stop it. Children with this acute disease often have multiple organ failure and receive several medications; therefore, these patients need to use intravenous anticonvulsant drugs with few complications or low drug interactions and this leads to the increased consumption of new anticonvulsant drugs such as Vimpat [2]. Vimpat (lacosamide) was confirmed by the European Union in August 2008 and by the US Food and Drug Administration in October 2008, as adjunctive therapy or monotherapy for partial and focal seizures in adolescents and adults aged at least 16 years (Europe) and 17 years (US), and in children with four years of

age and older that have epilepsy. It is used specifically as an antiepileptic drug and is available orally and intravenously [3, 4]. Vimpat is a functional amino acid that causes the gradual inactivation of voltage-dependent sodium channels, which over-stimulates nerve membranes, inhibits neuronal firing, and reduces the long-term availability of the channel without affecting physiological functions [5, 6]. Vimpat shows appropriate drug kinetic properties because it has little drug interaction and is, therefore, suitable for polytherapy and possibly for use in children [7]. Studies in this field indicate the effectiveness, tolerance, and safety of this drug in treating the children with epilepsy [8-12]. Due to the problems of epilepsy in children and the need to control and treat this disease, the present study aimed to provide a systematic review of published research evidence regarding the effectivness and tolerability of treatment with Vimpat (lacosamide) in children.

2. MATERIALS AND METHODS

This study is a systematic review, conducted by searching the databases of Elsevier, PubMed, Springer, and Wiley and with the keywords of status epilepticus, children, lacosamide, seizures, efficacy, and tolerability; these words were often used separately and in some cases as a combination of two words. Inclusion criteria were full-text articles in the field of effectiveness and tolerability of treatment with Vimpat (lacosamide) in patients, articles published after 2011, and articles published in English and exclusion criteria were articles without full-text, articles published before 2011, and review articles. In the analysis phase, the information collected from the studies consisted of the author (s), year, purpose, method of work, and research results. No interpretation was used during the data collection and the main phrases of the articles, which were used by the author (s), were mentioned.

3. RESULTS

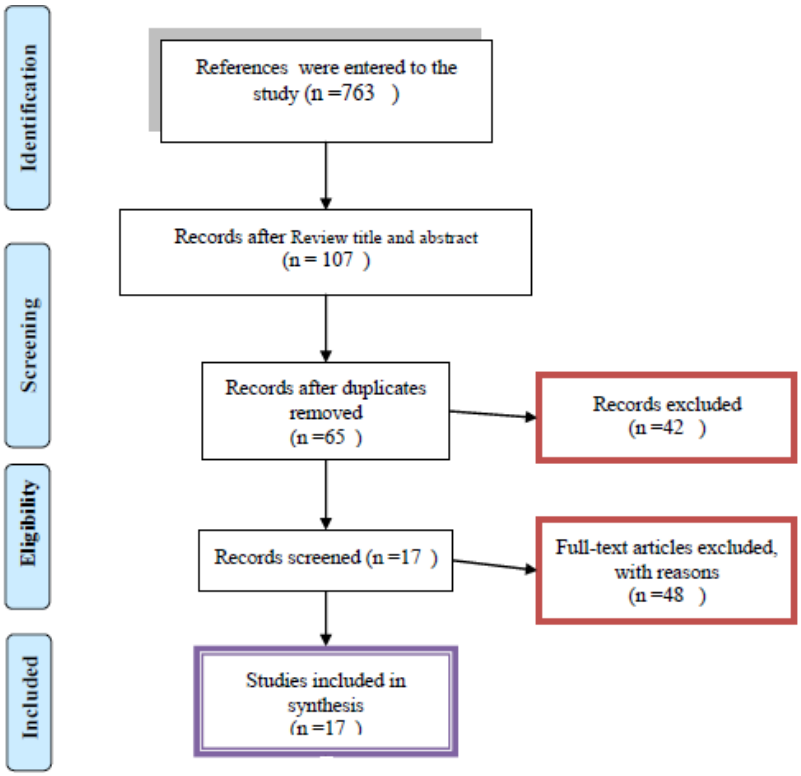

Figure 1 Diagram related to the selection of articles

In the initial phase, 763 titles were selected. At this stage, the title and, if necessary, the abstract of the articles was reviewed, and finally, 107 articles were selected. In the second phase, the full text of the articles was studied and 42 articles were removed due to duplication. Out of the remaining 65 articles, 48 articles were removed from the study based on the inclusion/exclusion criteria, and lastly, full texts of 17 articles published in English on the effectiveness and tolerability of treatment with Vimpat (lacosamide) in children, were selected for further review (Figure 1). The reviewed studies were conducted between 2011-2019.

The objectives and findings of these 17 studies are listed in Table 1. The results of these studies indicated the safety, effectiveness, and tolerability of the treatment with Vimpat in patients with epilepsy. This drug reduces the rate of seizures and improves the condition of pediatrics. A total of 949 epileptic children between the ages of less than 1 year and 18 years were studied in these 17 articles. The results showed that the use of lacosamide caused improvements in physical condition and reduced seizures in children. In 357 children (37.62%) side effects were observed following the consumption of this drug. These side effects included nausea, drowsiness, dizziness, blurred vision, worsening of seizures, behavioral abnormalities (aggression and depression), skin problems, ataxia (inability to coordinate muscle movement), and Bradycardia (decreased heart rate); however, most of these complications were minor and did not cause severe problems in children. The greatest effect of this drug in controlling and reducing status epilepticus was related to a study by Ngampoopun et al.; during this study, a 100% reduction was observed in seizures, within 24 hours [13]. On the other hand, the lowest efficacy of this drug was observed in a study conducted by Heyman et al., which reported a 35% reduction in seizures [14]. Among these 17 studies, the maximum follow-up time was 72 months [15] and the minimum was 12 hours [16]. Amongst the 17 studies related to the treatment of epilepsy in children with Vimpat medication, in 6 studies (35.3%) this drug was used as monotherapy, in 10 studies (58.82%) was used as polytherapy, and in 1 study (5.88) was used as a combination of these two treatments. The effectiveness of this drug as monotherapy was between 8.2% (in focal and generalized seizures) to 100% (in acute seizures) and as polytherapy was between 40% (in patients with partial epilepsy) to 90% (in patients with Lennox–Gastaut syndrome). In a study by Yorns et al [17] that this drug was used as a combination of monotherapy and polytherapy, a 76.5% reduction in seizure rate was seen.

Table 1: Results related to the effectiveness and tolerability of treatment with Vimpat (lacosamide)

Reference	**Title**	**Number of samples**	**Methods/ Dose/ Follow-up**	**Results**
Toupin *et al* (2015) [18]	Efficacy and safety of lacosamide as an adjunctive therapy for refractory focal epilepsy in pediatric patients: a retrospective single-centre study	22 children, 14 of whom were boys and 8 were girls, with an average age of 12.9 years	7.5 antiepileptic medications were formerly prescribed to patients, on average. The average number of concomitant antiepileptic medications was 2.3. The mean primary and retention dosages were 2.9 and 8.4 mg/kg/d, respectively. **follow-up:** 11.9 months.	Following 90 days of treatment and on the last follow-up visit, 13 patients (59 %) and 10 patients (45 %) were responders, respectively, and one of them was convulsion-free. In 11 patients, adverse effects were found and none were extreme. Considering all studied parameters except gender, responders and non-responders were equal, with the number of respondents being higher in girls compared to boys (75 percent vs 29 percent) (75 percent vs 29 percent).

Pasha *et al* (2014) **[19]**	Efficacy and tolerability of lacosamide as an adjunctive therapy in children with refractory partial epilepsy	79 children: 53 boys and 26 girls with an average age of 8.8 ± 3.1 years. Average weight of the patients was 24.2 ± 9.8 kg.	Lacosamide was used as an adjunctive treatment in patients, who formerly had used two or more antiepileptic medications that were ineffective. Lacosamide tablets were consumed orally at a dosage of 25 mg for 1 week, followed for the remaining duration by 50 mg twice a day. Effectiveness and tolerability assessment was conducted at each titration visit, maintenance period (3 months), and two follow-up visits at monthly intervals.	At the start of the seizures, the mean age was 6.4 ± 3.5 years. The average administered dosage of LCM was 4.1 mg/kg. Due to vomiting, hostile behavior, and inadequate response to the treatment, three patients (3.8%) were excluded from the study. Among the 76 children (96.2%) who entered the retention phase, 35 patients (44.3%) had no seizures, 32 patients (40.6%) showed ≥50 % decrease in seizure frequency, 3 patients (3.8%) demonstrated 25-49% decrease in seizure frequency, and 9 patients (11.4%) either had no improvement in seizures or showed increment of seizures.
Farkas *et al* (2019) **[20]**	Efficacy and tolerability of adjunctive lacosamide in pediatric patients with focal seizures	343 children with 4 to 17 years of age	Cases who had the target dosage range based on their weight (<30 kg: 8-12 mg/kg/d oral solution; <30-<50 kg: 6-8 mg/kg/d oral solution; <50 kg: 300-400 mg/d tablets), after a 6-week titration, entered a retention period of 10 weeks. The initial result was a decrease in focal seizure frequency after 28 days from the first stage to the retention phase.	346 patients were randomized; From the initial stage to the maintenance phase, the percentage of reduction in focal seizures after twenty-eight days of treatment with lacosamide (170 people) vs placebo (168 people) was 31.7%. In the maintenance phase, the median percentage of reduction in focal seizures after twenty-eight days of treatment was 51.7% for the group of patients that received lacosamide and 21.7% for the control group. 50% response rates (≥50% reduction in seizure frequency) were 52.9% and 33.3% (odds ratio 2.17), respectively. During treatment, treatment-emergent AEs were found in 67.8% of children that were treated with LCM (58.1% in group group), most commonly (≥10%) somnolence (14.0%, control 5.2%) and dizziness (10.5%, control 3.5%).
Grosso *et al* (2014)**[21]**	Efficacy and safety of lacosamide in infants and young children with refractory focal epilepsy	24 children with a mean age of 2/7 years	Vimpat was combined with the initial treatment at a primary dosage of 1-2 mg/kg/day and titrated to the final dosage at a range of 7 to 15.5 mg/kg/day. Effectiveness was assessed after 90 days of treatment. **follow-up**: 12 months	After at least 90 days of combination treatment with Vimpat, 10 children (42%) were respondents to the treatment (≥50% reduction in seizures) and 4 of them (17%) had no seizure. Maintenance rate, after at least 12 months of treatment with LCM, was assessed in a group of 18 patients. In the latter group, 8 children (44%) were initial respondents (3 of them had no seizures). After 12 months of follow-up, 4 children

				(22%) maintained the improvement and 2 (11%) of them remained seizure free. A loss of effectiveness was seen in 4 of the initial respondents (50%). Unfavorable complications were observed in 8 (33%) children.
Kim *et al* (2014) **[22]**	Lacosamide as an adjunctive therapy in pediatric patients with refractory focal epilepsy.	21 children: 16 boys and 5 girls with an average age of 13/9 years	3.0 (1-6) concomitant antiepileptic medications were used on average and the average retention dosage of Vimpat was 5.4 (1.4-9.8) mg/kg/day. **The average time of follow-up:** 10.1 months.	14 patients (67%) responded well to the treatment and four of them had no seizure at the last follow-up. 7 patients (33%) did not respond to the treatment, 2 of them showed <50% decrease reduction in seizures and 5 demonstrated no change in seizures. Two patients (10%) discontinued the consumption Vimpat, due to adverse side effects (hostile behaviors and depression). Mild complications were seen in 8 of the 21 patients (38%).
Miskin *et al* (2016) **[23]**	Efficacy and Tolerability of Lacosamide in the Treatment of Children with Refractory Generalized Epilepsy	21 children: 11 boys and 10 girls with an average age of 11/9 years	Children were divided into 2 groups; the first group were children with Lennox-Gastaut Syndrome, and the second group were patients with other generalized epilepsies. Effectiveness was defined as cessation of seizures or more than 50% decrease in seizures. Descriptive data analysis including cessation of seizures rate was performed using c(2) analysis.	5 patients had no seizures, 9 demonstrated >50% decrease in seizures, and 7 did not respond to the treatment. In the first group 7 had more than 50% improvement and 1 was non-respondent. In the second group 5 had no seizures, 2 showed more than 50% improvement, 5 were non-respondents. Vimpat had good efficacy and was well tolerated in patients with refractory generalized epilepsy particularly in children who had Lennox-Gastaut Syndrome.
Yorns *et al* (2014) **[17]**	Efficacy of lacosamide as adjunctive therapy in children with refractory epilepsy	40 children with a mean age of 14/3 years	lacosamide treatment was used in children (polytherapy in 36 children, monotherapy in 4 children). Mean dosage was 7 mg/kg/d. **Mean follow-up:** 9.2 months	Symptomatic focal epilepsy was seen in 15 children, cryptogenic focal epilepsy was observed in 2 children, symptomatic generalized epilepsy was observed in 20 children, and cryptogenic generalized epilepsy was seen in 15 patients. Juvenile myoclonic epilepsy was seen in 2 patients and Lennox-Gastaut syndrome was observed in 5 children. 42% of the patients showed a minimum of 50% decrease in seizures, and 6 became seizure-free. Respondents had a 76.5% average reduction in seizures. 15 patients had adverse complication and 7 discontinued the consumption of Vimpat (4 due to Inefficacy of treatment, 1 due to insurance denial, 1

				tremor, and 1 due to hostile behaviors).
Rastogi and Ng (2012) **[24]**	Lacosamide in refractory mixed pediatric epilepsy: a prospective add-on study	21 children. Age: <17 years	5 children were removed from study, since they had lower than 90 days of significant follow-up. Retention doses were between 2.4 to 19.4 mg/kg/d.	Among the sixteen children that were studied, 8 (50%) had more than 50% decrease in seizures following the add-on treatment with lacosamide. Generalized epilepsy was seen in 8 children (50%) and 4 of which had Lennox-Gastaut syndrome. Vimpat was effective in the treatment of most seizure types, particularly partial-onset seizures. Treatment with Vimpat was effective in 5 of 8 children (62.5%) with local epilepsy, however, in only 2 of 8 children (25%) with generalized epilepsy this treatment was effective; Both children with Lennox-Gastaut syndrome demonstrated more than 90% reduction in seizures. None of the patients with refractory epilepsy remained seizure-free.
Guilhoto *et al* (2011) **[25]**	Experience with lacosamide in a series of children with drug-resistant focal epilepsy	16 children: 7 boys and 9 girls with a mean age of 14/9 years	Children had formerly received a median of 2 antiepileptic medications (interquartile range 1.7-3). Also, 3 patients had undergone former epilepsy surgery, VNS was performed in 9 patients, and 3 had ketogenic diet**. median dose of lacosamide** was 275 mg daily, 4.7 mg/kg daily. **median follow-up** :4 months	Seizures were caused by structural abnormalities (encephalomalacia in 1 patient, diffuse encephalitis in 1 patient, and stroke in 2 patients) or genetic abnormalities (one Aarskog and one Rett syndromes) or the cause was unknown (in ten patients). Seizures averagely occurred 57 times per month at the initial phase and after a mean follow-up period of 120 days following the consumption of Vimpat, it was 12.5 per month. 6 children (37.5%; 3 seizures-free) were to respondents the treatment (more than 50% decrease in seizures) and 10 were non-respondents (less than 50% reduction in 3, increase in 1, and no change was seen in 6 children). Adverse complications (tics, hostile behaviors, exacerbation of seizures, and depression with suicidal ideation in 1 patient each) prompted LCM discontinuation in four of sixteen patients (25%).
Gulati *et al* (2015) **[26]**	Lacosamide as adjunctive therapy in treatment-resistant	40 patients age range: 2-19 years	Electroencephalograms of all of these children contained abnormalities, and 36 of them had malformed neuroimaging. All patients	RR was observed in 20% with maintenance of RR in 8/36, 8/30 and 8/26 children that were treated with lacosamide at 3-, 6- and 9-month follow-up. 2

	epilepsy in childhood		had more than 2 failures in AED trials, 9 had ketogenic diet, 5 had failure in vagus nerve stimulation and 11 had failure in resective surgery. Average dosage and duration of treatment with lacosamide were 5.7 mg/kg/day and 10.5 months, respectively. **follow-up:** 3, 6 and 9 months.	patients had no seizures. Maintenance on lacosamide was 65% at 9 months. Vimpat was well tolerated with insignificant complications in 7 patients; no patient discontinued lacosamide due to complications.
Casas-Fernández *et al* (2012) **[27]**	Efficacy and tolerability of lacosamide in the concomitant treatment of 130 patients under 16 years of age with refractory epilepsy: a prospective, open-label, observational, multicenter study in Spain	130 patients aged 6 months to 16 years	Lacosamide was initially consumed twice a day as an oral solution or as an oral tablet, with a primary dosage of 1-2 mg/kg/day in most cases. Most of the children were also receiving permanent concomitant medications with ≥1 other AEDs. The average dosage of LCM was 6.80 ± 2.39 mg/kg/day. **follow-up:** 3 months	After 3 months of treatment with LCM, 62.4% of children had more than 50% reduction in seizures and 13.8% of children were seizure-free. Unfavorable complications were seen in 39 children (30%), but no association between dosage and response rate was seen, based on these complications. In ten patients, issues of instability, loss of balance, problems with subjective elements, blurred vision, and dizziness were noted. Of the 13 patients who received the drug, 5 discontinued treatment due to a lack of response, and 4 of these patients ultimately required treatment discontinuation. There were major differences in symptoms in each patient making the determination difficult.
Arkilo *et al* (2016) **[16]**	Clinical experience of intravenous lacosamide in infants and young children	47 children with a median age of six-and-a-half. 18 were less than three years old, of which 8 were younger than twelve months old.	Lacosamide was consumed intravenously for the treatment of epilepsia partial is continua (in 3 patients, dosage range of 5mg/kg), status epilepticus (11 patients, median dosage of 7 mg/kg, range 4–10 mg/kg), and acute exacerbation of seizures (18 patients, median dosage 4.4 mg/kg, range 1–11 mg/kg). **Outcome (hours):** 12	Parenteral administration was used instead of oral consumption for 10 patients treated with retention lacosamide that could not ingest/tolerate enteral drug and 5 who received intravenous lacosamide to begin retention therapy (mean dosage 4 mg/kg, range: 2–10 mg/kg). The efficiency of injection was observed in 24 of 37 patients (65%) that were sensitive to lacosamide. Sedation (one with ataxia) was seen in 5/36 patients (14%), without any other significant complications.
Grosso *et al* (2014) **[28]**	Lacosamide in children with refractory status epilepticus. A multicenter Italian experience	11 patients with an average age of 9.4 years	All patients failed to respond to the treatment, after standard protocols before the intravenous LCM treatment. The mean initial dosage of LCM was 8.6 mg/kg and **follow-up:** 24 hours	Symptoms were observed in 7 children (63 percent). RSE was convulsive (focal or generalized) in 6 children, while in 5 patients it was nonconvulsive. The primary average dosage of lacosamide was 8.6 mg/kg. The drug could

				be used as a fourth or later option to treat RSE in 45 percent of children and three children who were treated were seizure-free within 12 hours. No significant complication occurred as a direct result of LCM.
Rosati *et al* (2018) [15]	Long-term efficacy of add-on lacosamide treatment in children and adolescents with refractory epilepsies: A single-center observational study	88 children: 47 boys and 41 girls. Aged: 4 months to 18 years.	Treatment with LCM was implemented as an adjunctive therapy for refractory focal and generalized epilepsy. **follow-up:6-72** months	34 children (38.6%) were responded to the treatment with a mean recurrence time of 48 months. 9 (26.4%) of the 34 respondents had no seizures. Among all 88 children, the possibility of remaining on lacosamide without add-on treatment was 74.4% at 6 months, 47.7% at 12 months, 27.9% at 24 months, 18.0% at 48 months, and 8.2% at 72 months of follow-up. No differences in recurrence and maintenance time were seen, considering epilepsy and seizure types, duration and course of epilepsy, number, and type of antiepileptic drugs. The most frequent unfavorable complications were dermatological (4/11) and behavioral (3/11).
Gavatha *et al* (2011) **[29]**	Efficacy and tolerability of oral lacosamide as adjunctive therapy in pediatric patients with pharmacoresistant focal epilepsy	18 children. Age: 3-18 years.	LCM was used orally, and the final dosage, following slow titration, ranged between 1.7 and 10 mg/kg. average period of treatment was 8 months. **follow-up:** 3 months	Effectiveness of the therapy was evaluated 2 times with a 1-year interval. >50% decrease in seizures was seen in 36% patients in the primary short-term point and in 20% of cases at the following long-term evaluation. Adverse effects, mostly somnolence and irritability, were observed in 39% of children in both assesments.
Heyman *et al* (2012) **[14]**	Preliminary efficacy and safety of lacosamide in children with refractory epilepsy	17 patients: 10 boys and 7 girls. Aged: 1.5-16 (average 8 ± 4.7) years	**LCM with an average dosage** of 6.80 ± 2.39 mg/kg/day was used. **The mean duration of follow-:** 9.1 ± 4.4 months.	Epilepsy was caused by structural abnormalities in 9 children, had unknown cause in 6 children, and 2 children had had Lennox-Gastaut syndrome. Average duration of epilepsy was 5.4 ± 3.3 years. Average number of formerly consumed AEDs was 6.6 ± 2. LCM was added to the initial AEDs in 13 children. 6 (35%) patients had a minimum of 50% reduction in seizures (76% on average). Social, behavioral, and motor improvements were observed in 7 children (41%). The consumption of LCM was

				stopped in 6 children (35%) due to ineffectiveness. complications were noted in 10 children (59%).
Ngampoopun *et al* (2018) **[13]**	Effectiveness and Adverse Effect of Intravenous Lacosamide in Nonconvulsive Status Epilepticus and Acute Repetitive Seizures in Children	11 children: 3 boys and 8 girls with an average age of 11 years	Mean loading dosage was 227 mg (8.3 mg/kg/dose) and mean daily retention dosage was 249 mg (4.6 mg/kg/dose). **follow-up:** 24 hours	A reduction in seizures was observed in all children in 24 hours. Eight of eleven patients showed >50% decrease in seizures at the final phase of the research, and 1 child had no seizure. Considering the complications, 1 child had a bradycardia without prolongation of the PR interval. One patient had neuronal ceroid lipofuscinosis and showed significant improvements in controlling seizures by the end of the research.

4. DISCUSSION

The objective of this research was to conduct a systematic review of published articles regarding the effectiveness and tolerability of treatment with Vimpat (lacosamide) in children. Out of a total of 763 studies with topics similar to the above, 17 articles were finally selected for further review. By studying these articles, it was found that the consumption of LCM in children with epilepsy reduces seizures and improves the process of control and treatment of this disease. The greatest effect of this drug was observed in children with acute generalized seizures (status epilepticus) and especially children with Lennox–Gastaut syndrome with 100% [13] and 90% [24] efficacy. In the following, we will review these studies. A study by Toupin et al., which aimed to assess the effect and safety of lacosamide as adjunctive therapy in 22 patients with an average age of 12.9 years with focal epilepsy who had formerly received antiepileptic drugs, showed that 59% And 45% of patients responded to this treatment after 90 days of treatment with this drug and at the last follow-up visit (mean 11.9 months), respectively, and in one child the cessation of seizures was observed. Side effects were observed in eleven children, which were not severe. The average number of concomitant AEDs was 2.3 and the average of primary and retention dosages were 2.9 and 8.4 mg/kg/d, respectively [18]. A research by Pasha et al. on 79 patients with an average age of 8.8 ± 3.1 years with refractory partial epilepsy showed that the use of lacosamide at a mean dosage of 4.1 mg/kg led to a cessation of seizure in 44.3% of children, more than 50% reduction in seizures in 40.6% of children, and 25-49% reduction in seizures in 3.8% of children. On the other hand, 11.4% of these children either showed no changes in seizures or had an increase. These children had previously received two or more antiepileptic drugs, and due to their ineffectiveness, Vimpat was used as an adjunct. During this study, three patients (3.8%) were excluded from the study due to nausea, aggressive behavior, and poor response [19]. Farkas et al. conducted a study on 343 patients aged 4-17 years to evaluate the effectiveness and tolerability of add-on LCM treatment in patients with focal seizures. These cases were divided into two subgroups: receiving Vimpat and placebo. The dose of this drug was different according to the weight of children; for children weighing less than 30, between 30-50 and more than 50 kg, the prescribed dosages were 8-12 mg/kg/d (as an oral solution), 6-8 mg/kg/d (as an oral solution), and 300-400 mg/d (as tablets), respectively. The results of this study indicated that a 50% reduction in seizures was observed in 52.9% of children in the Vimpat group and 33.3% of children in the placebo group. Also, from the beginning to

follow-up (10 weeks), the rate of reduction in the frequency of focal seizures every 28 days for Vimpat (170 patients) versus placebo (168 patients) was 31.7%. During the follow-up period, the average percentage of decrease in the frequency of focal seizures every 28 days was 51.7% in the treatment group and 21.7% in the control group. Complications were observed in 67.8% of children treated with lacosamide and in 58.1% of the placebo group. The main side effects were drowsiness and dizziness [20]. The study by Grosso et al., which aimed to assess the effectiveness and safety of Vimpat in patients with refractory focal epilepsy and studied 24 patients with a mean age of 2.7 years, showed that after at least three months of lacosamide treatment as adjunctive therapy, 10 patients (42%) had an appropriate response to the treatment (≥50% decrease in seizures) and among them, seizures were stopped in 4 patients (17%). The duration of action of this drug after at least 12 months was evaluated in a group of 18 people, of which 8 patients (44%) responded to this treatment, 3 of whom were without seizures. After 12 months of follow-up, in four children (22%) the improvements were preserved and 2 of them (11%) showed no seizures; loss of effect of this drug was observed in 4 primary respondents (50%). In this research, Vimpat was added to the initial treatment with a starting dosage of 1-2 mg/kg/d and the final dosage ranged from 7-15.5. Side effects following the consumption of this medication were observed in 8 children (33%) [21]. A research by Kim et al. on 21 children with an average age of 13.9 years with focal epilepsy showed that the use of lacosamide as adjunctive therapy at an average dosage of 5.4 mg/kg caused 14 children (67%) to appropriately respond to the treatment and four of them had no seizures at the last follow-up (mean 10.1 months). 7 patients (33%) did not respond to this treatment, 2 of whom had a reduction of less than 50% in seizures and 7 patients did not show any changes in seizures. Two patients (10%) discontinued oral Vimpat due to side effects (aggressive behavior and depression). Mild side effects associated with this treatment were observed in 8 patients (38%). Also, the average number of concomitant AEDs before the consumption lacosamide was three [22]. Miskin et al. conducted a study to evaluate the effectiveness and tolerability of Vimpat in 21 patients with a mean age of 11.9 years with generalized epilepsy, during which children were divided into 2 subgroups: Group 1: Children with Lennox-Gastaut syndrome and group 2: Children with other generalized epilepsies. The findings of this research demonstrated that 5 patients affected by this drug did not have seizures (23.81%), 9 patients had more than 50% reduction in seizures (42.86%) and 7 patients (33.33%) did not respond to this medication. In group 1, 7 children improved more than 50% and 1 did not respond to Vimpat. In group 2, 5 patients had no seizures after using the drug and 2 patients had more than 50% improvement, on the other hand, 5 patients did not respond to this medication. The finding of this research demonstrated that LCM was effective and well tolerated in patients with generalized epilepsy, especially in patients with Lennox-Gastaut syndrome [23]. Yorns et al. preformed a research to assess the efficacy of lacosamide on 40 epileptic children with an average age of 14.3 years. 15 patients had symptomatic focal epilepsy, 2 had cryptogenic focal epilepsy, 20 had generalized symptomatic epilepsy, and 3 had cryptogenic generalized epilepsy. Also, two had juvenile myoclonic epilepsy and five had Lennox-Gastaut syndrome. In 36 children, Vimpat was consumed as an add-on treatment (polytherapy) and in 4 patients as the main treatment (monotherapy) with an average dosage of 7 mg/kg. Finding of this study showed that 42% of children had a 50% decrease in seizures and 6 were seizure-free. Respondents to lacosamide had an average reduction rate of 76.5% in seizures. Adverse reactions were observed in 15 children due to the use of this drug and in 7 cases its consumption was stopped (4 patients showed no efficacy, 1 patient did not have insurance, 1 patient had tremor, and 1 patient had behavioral disorders). The average follow-up time in these children was 9.2 months [17]. The results of a study by Rastogi and Ng on 21 children and adolescents under 17 years of age who had refractory focal and generalized epilepsy showed that the use of lacosamide as

adjunctive therapy at doses of 2.19 - 4.4 mg/kg, caused more than 50% reduction in seizures, and this efficacy was observed in 50% of children. 50% of children had generalized epilepsy, of which 4 had Lennox-Gastaut syndrome. The results indicated that Vimpat was effective for the treatment of most types of seizures, especially for seizures with focal initiation. LCM was effective in the treatment 5 patients with focal seizures, whereas this effect was seen in only 2 of 8 children with generalized seizures (25%). Also, both patients with Lennox-Gastaut syndrome, who were treated with this medication, demonstrated > 90% decrease in seizures. None of these children with refractory epilepsy remained resistant to seizures. Five children were excluded from the study due to a follow-up period of fewer than 90 days [24]. Guilhoto et al. preformed a research on 16 children with an average age of 14.9 years with refractory focal epilepsy to assess the effect of Vimpat as an adjunctive therapy. Structural abnormalities were the cause of epilepsy in 4 children (1 seizure due to encephalitis and in two other cases seizures with unknown etiology); in 2 cases the seizures were caused by genetic abnormalities (Rett and Aarskog syndromes) and in 10 children cause of the disease was unclear. In addition to having previously undergone surgery (3 cases), vagus nerve stimulation (9 cases), and a ketogenic diet (3 cases), these children were consuming an average of two AEDs. The findings of this research showed that the mean seizure frequency was initially 57 seizures per month and after 4 months of using LCM (with a mean dosage of 4.7 mg/kg/d) this rate was reduced to 12.5 seizures per month. In total, this drug caused a 50% reduction in seizures in 6 patients (37.5%), of which 3 were without seizures. 10 people did not respond well to this medication (reduction of less than 50% in 3 patients, increase in seizures in 1 patient (who had Rett syndrome), and 6 patients showed no changes in seizure frequency). In 6 children, side effects (behavioral disorders, worsening of seizures, and depression with suicidal ideation) were observed following the use of Vimpat, which led to discontinuation of the drug in 4 (25%) of children [25]. A study was conducted by Gulati et al. to assess the efficacy of add-on therapy using lacosamide in 40 children and adolescents aged 2-19 years with refractory epilepsy (36 patients had focal or multifocal seizures according to their EEG and 4 Patients had bilateral convulsive waves including 1 patient with Down syndrome, 1 patient with hypothalamic hamartoma, 1 patient with channelopathy, and 1 patient with generalized cryptogenic epilepsy). The results of this research showed that in the first 3 months 22%, in the sixth month 26%, and in the ninth month 30.7% of children responded well to the treatment with lacosamide (with an average dosage of 5.7 mg/kg/d); the duration of the effect of Vimpat in the ninth month was equal to 65%. In 7 children, minor side effects of LCM were observed that were well tolerated and no child stopped the consumption of this drug due to side effects. All children were treated with more than 2 antiepileptic drugs (mean 2.7 drugs) prior to LCM treatment, none of which were effective. Nine people underwent a ketogenic diet, five underwent vagus nerve stimulation, and 11 underwent resection surgery, and all of these methods failed. In this study, it was hypothesized that if lacosamide treatment did not lacosamide and epilepsy syndrome. In addition, no cardiovascular complications were observed and no changes were reported in routine post-drug testing. Also, more effectiveness was observed in the treatment with a combination of lacosamide and an anticonvulsant drug respond within 3 months after starting the drug, it would be unreasonable to continue lacosamide treatment [26]. Casas et al. preformed a research on 130 patients aged 6 months to 16 years with refractory epilepsy to evaluate the effectiveness of Vimpat. LCM was initially administered twice a day as an oral solution or as an oral tablet with a primary dosage of 1-2 mg/kg/d. Most children were treated with more than one other AED at the same time. The results of this study showed that after 3 months of treatment with Vimpat (at a dose of 80.6 ± 2.39 mg/kg/day), 62.3% of patients achieved a reduction of more than 50% in the frequency of seizures, while complete suppression of seizures was seen in 13.8% of cases. Complications were observed in 39

children (30%), of which 10 reported weakness, walking abnormalities, mental incapacity, blurred vision, or dizziness, and the treatment was discontinued in 13 patients. In 5 children, despite dose reduction, the severity of symptoms remained unchanged, which also led to cessation of the therapy. In this study, no association was found between the response to a corelative mechanism of action, such as levetiracetam. On the other hand, the use of lacosamide with other medication that affect sodium channels (e.g., benzodiazepine, carbamazepine, ethosuximide, lamotrigine, oxcarbazepine, phenytoin, phenobarbital, topiramate, or zonisamide) was less effective in this research. [27]. A study was conducted by Arkilo et al. to assess the effect of adjunctive therapy using intravenous LCM in 47 patients with an average age of 6.5 years with epilepsy. Intravenous lacosamide was used to control epilepsia partialis continua in three patients,[30] status epilepticus in 11 patients, acute exacerbation of seizure frequency in 18 patients, and to replace the oral form in 10 patients who could not tolerate the oral form; also, it was used to start the treatment with loading dose in 5 patients. The results showed that LCM injection was effective in 24 of 37 children (65%). Drowsiness was observed in 5 out of 36 children (14%) without any other side effects. The mean dose of intravenous LCM for the treatment of partial epilepsy was 5-10 mg/kg (3 patients), for the treatment of epileptic crisis or stable epilepsy was 4-11 mg/kg (11 children), and for the treatment of exacerbation of seizures was 1-11 mg/kg (18 children). In this study, 46 children had focal seizures and one patient had generalized seizures. In 26 children, seizures were due to metabolic or structural abnormalities, in 12 cases due to genetic abnormalities, and in 9 cases there was no cause [16]. In a study by Grosso et al. to assess the effect of add-on therapy using intravenous lacosamide in 11 children with an average age of 9.4 years with refractory epilepsy, it was shown that LCM (initial dose 8.6 mg/kg) was used as the fourth or later option; it was effective in 45% of children and in 3 cases the seizures ended within 12 hours. No complication was observed following the use of LCM. Prior to the use of this drug (intravenously) all previous treatments had failed. 6 children had convulsive epilepsy (focal or generalized) and 5 children had non-convulsive epilepsy [28]. Rosati et al. assessed the long-term effect of add-on treatment with lacosamide in 88 children (4 months to 18 years of age) with refractory epilepsy. The results of this study showed that 34 patients (38.6%) responding to this drug had a mean recurrence of 48 months. Nine (26.4%) of 34 respondents had no seizures. On the other hand, the probability of the effect of this drug without adjuvant treatments (taking Vimpat before drugs blocking sodium channels or other drugs) in 6, 12, 24, 48, and 72 months was equal to 74, 47.7, 27.9, 18, and 8.2%, respectively. 57 patients (64.7%) with refractory focal seizures, 13 patients (14.7%) with generalized epilepsy, and 18 patients (20.5%) with mixed epilepsy (focal and generalized) received lacosamide as adjunctive therapy. Considering the type of epilepsy and seizures, period and duration of epilepsy, and the number and type of AEDs, no differences were seen in recurrence and duration of drug effect. Out of 34 children who were respondents to this medication, the seizure-free rate after 6, 12, 36, and 72 months was 1.94%, 8.84%, 8.66%, and 3.31%, respectively. The mean recurrence time for respondents with focal, generalized, and mixed seizures were 45,49, and 37 months, respectively. Overall, approximately 40% of the 88 patients treated with lacosamide responded to treatment, and only one-third of those respondents were still responding after 72 months of follow-up. The most common side effects were skin complications (4 out of 11 people) and behavioral disorders (3 out of 11 people) [15]. A study by Gavatha et al. On 18 children aged 3-18 years with refractory focal epilepsy found that the rate of reduction in seizures following the use of Vimpat (monotherapy) at a dosage of 1.10-7 mg/kg was equal to 36% in the short-term and below 20% in the long-term assessment. These patients were taking 1-3 other anticonvulsants at the same time and had a history of taking 3-16 anticonvulsants (mean 7 drugs) before. One patient did not improve with VNS, one patient had more seizures after the epilepsy surgery,

and in three patients ketogenic diet caused no improvement. In 13 patients the epilepsy was due to a structural abnormality of the brain (2 patients with cortical dysplasia, 2 patients with CNS malformation, 2 patients with the neurocutaneous syndrome, one patient with hippocampal sclerosis, and 5 patients with perinatal ischemic lesions) and in 5 other cases, the cause was unknown. The mean duration of lacosamide treatment was 8 months (3 weeks to 17 months). 50% of the children were receiving concomitant sodium channel blockers at the same time. Most of the children received valproate (45%) and levetiracetam (39%) at the same time. In the first evaluation, only 14 patients received medication for at least 3 months, with 5 patients (36%) having ≥50% decrease in seizures. One year after the first evaluation, a reassessment was performed at which time only 4 patients were still receiving lacosamide and three patients (20%) showed > 50% decrease in seizures. In 39% of cases, complications including drowsiness and mood disorders were observed in both assessments (short-term and long-term) [29]. The study by Heyman et al. on 17 children aged 1.5-16 years with refractory epilepsy showed that following the use of LCM with an initial dosage of 4.5-5 mg/kg and a highest dosage of 7.6-20 mg/kg, 6 patients (35%) had a minimum of 50% decrease in seizures (average 76%). Also, social, behavioral, and motor improvements were observed in 7 children (41%). In 6 patients (35%) Vimpat was discontinued due to inefficiency and in 10 patients (59%) side effects were reported. In this research, 9 children had structural epilepsy, 6 patients had unknown epilepsy, and two had Lennox-Gastaut syndrome. Twelve patients had focal seizures, of which 3 children had bilateral generalized seizures and 5 children had both focal seizures and generalized seizures. The mean duration of epilepsy was 5.4 ± 3.3 years. The average number of former AEDs (antiepileptic drugs) was 6.6 ± 2. In 13 patients LCM was added to the initial AEDs [14]. Ngampoopun et al assessed the effectiveness and adverse effects of intravenous LCM on non-convulsive status epilepticus and acute repetitive seizures in 11 patients with a mean age of 11 years. The findings of this research showed that after using LCM with an average loading dose of 8.3 mg/kg/d and retention dosage of 4.6 mg/kg/d, all children showed a decrease in seizures 24 hours after the treatment. 8 out of 11 patients (72.7%) had more than 50% reduction in seizures at the end of the study and 1 child had no seizures. Considering the side effects, 1 patient developed bradycardia. In this study, neuronal ceroid lipofuscinosis was observed in one patient, who had significant improvements in seizure control after the treatment [13]. In addition, the effect and safety of this drug have been reported in other studies [31-34]. In a research by Afra et al., 3 patients with clinical and electrographic symptoms of juvenile myoclonic epilepsy were treated with lacosamide (in one patient as monotherapy and in two patients as adjunctive therapy). None of these patients had myoclonus worsening, and in one patient intermittent myoclonic twitches responded to an increase in lacosamide dose [31].

On the other hand, in 357 children studied in these 17 articles (37.62%), side effects following the use of this drug were observed and the rate of these side effects in studies in which Vimpat was used as monotherapy was less, in comparison with the studies that used this medication as polytherapy; so that the most side effects in the first type of treatment were 39% [29] and in the second type of treatment were up to 59% [14]. In these 17 studies, the follow-up time varied from 12 hours [16] to 72 months [15]. In 3 studies, a direct association was observed between the follow-up time and the response and efficacy of the drug on children [15, 26, 29].

Uncontrolled seizures could be seen in about 25-30% of epileptic children despite treatment with antiepileptic drugs (AEDs) [20]. These children are at risk for several neurological and psychological disorders, which might be due to the consumption of certain AEDs [35]. Therefore, finding treatments with the new AEDs is essential, and one of these drugs is Vimpat (lacosamide) [20]. Vimpat is an antiepileptic drug that has been approbated in the United States and Europe as an adjunct therapy for partial seizures. Studies show that

this drug may interfere with the collapsin response mediator protein 2 (CRMP2). The effect of LCM in animal models of epilepsy and phase II / III clinical trials has been demonstrated. Pharmacokinetic studies found that Vimpat is excreted by the kidneys, binds to plasma proteins, and has no clinical drug-interactions. Clinical trials have shown that this drug is well tolerated in patients [36]. Initially, this drug was considered due to its high oral potential and stereoselectivity. At present, from a clinical point of view, Vimpat (lacosamide) is the only known antiepileptic drug that exerts its anticonvulsant activity mainly by selectively increasing the gradual inactivation of the sodium channel [37].

5. CONCLUSION

Although during this systematic review it was shown that the consumption of lacosamide in children with epilepsy decreases seizure frequency and improves the process of control and treatment of this disease, due to some side effects of this drug, major studies are required, in order to assess the effectiveness, tolerability, and safety of this medication, and to determine the appropriate doses of this medication for children.

6. REFERENCES

[1] Dalziel SR, Borland ML, Furyk J, Bonisch M, Neutze J, Donath S, Francis KL, Sharpe C, Harvey AS, Davidson A, et al. Levetiracetam versus phenytoin for second-line treatment of convulsive status epilepticus in children (ConSEPT): an open-label, multicentre, randomised controlled trial. *Lancet*. 2019; 393(10186): 2135-45. doi:10.1016/s0140-6736(19)30722-6

[2] Welsh SS, Lin N, Topjian AA, Abend NS. Safety of intravenous lacosamide in critically ill children. *Seizure*. 2017;52:76-80. doi:10.1016/j.seizure.2017.09.019

[3] Verrotti A, Loiacono G, Pizzolorusso A, Parisi P, Bruni O, Luchetti A, Zamponi N, Cappanera S, Grosso S, Kluger G, et al. Lacosamide in pediatric and adult patients: comparison of efficacy and safety. *Seizure*. 2013; 22(3): 210-6. doi:10.1016/j.seizure.2012.12.009

[4] Hoy SM. Lacosamide: A Review in Focal-Onset Seizures in Patients with Epilepsy. *CNS drugs*. 2018; 32(5): 473-84. doi:10.1007/s40263-018-0523-7

[5] Strzelczyk A, Zöllner JP, Willems LM, Jost J, Paule E, Schubert-Bast S, Rosenow F, Bauer S. Lacosamide in status epilepticus: Systematic review of current evidence. *Epilepsia*. 2017; 58(6): 933-50. doi:10.1111/epi.13716

[6] Tavasoli A, Gharib B, Alizadeh H, Farshadmoghaddam H, Memarian S, Ashrafi M, Sharifzade M. Brain on FIRES: Super Refractory Seizure in a 7 yr Old Boy. *Iranian journal of child neurology*. 2016;10(4):80-5.

[7] Pasha I, Kamate M, Suresh DK. Safety of lacosamide in children with refractory partial epilepsy. *Saudi pharmaceutical journal: SPJ: the official publication of the Saudi Pharmaceutical Society*. 2015; 23(5): 556-61. doi:10.1016/j.jsps.2015.01.006

[8] Ortiz de la Rosa JS, Ladino LD, Rodríguez PJ, Rueda MC, Polanía JP, Castañeda AC. Efficacy of lacosamide in children and adolescents with drug-resistant epilepsy and refractory status epilepticus: A systematic review. *Seizure*. 2018; 56: 34-40. doi:10.1016/j.seizure.2018.01.014

[9] Jain V, Harvey AS. Treatment of refractory tonic status epilepticus with intravenous lacosamide. *Epilepsia*. 2012; 53(4): 761-2. doi:10.1111/j.1528-1167.2012.03419.x

[10] Mnatsakanyan L, Chung JM, Tsimerinov EI, Eliashiv DS. Intravenous Lacosamide in refractory nonconvulsive status epilepticus. *Seizure*. 2012; 21(3): 198-201. doi:10.1016/j.seizure.2011.12.008

[11] Shiloh-Malawsky Y, Fan Z, Greenwood R, Tennison M. Successful treatment of childhood prolonged refractory status epilepticus with lacosamide. *Seizure*. 2011; 20(7): 586-8. doi:10.1016/j.seizure.2011.03.005
[12] Farshadmoghadam H, Pourakbari B, Mahmoudi S, Sadeghi RH, Mamishi S. Human herpesvirus 6 infection in febrile children: frequency in an Iranian referral hospital. *British journal of biomedical science*. 2014; 71(3): 108-10. doi:10.1080/09674845.2014.11669974
[13] Ngampoopun M, Suwanpakdee P, Jaisupa N, Nabangchang C. Effectiveness and Adverse Effect of Intravenous Lacosamide in Nonconvulsive Status Epilepticus and Acute Repetitive Seizures in Children. *Neurology research international*. 2018; 2018: 8432859. doi:10.1155/2018/8432859
[14] Heyman E, Lahat E, Levin N, Berkovitch M, Gandelman-Marton R. Preliminary efficacy and safety of lacosamide in children with refractory epilepsy. *European journal of paediatric neurology: EJPN: official journal of the European Paediatric Neurology Society*. 2012; 16(1): 15-9. doi:10.1016/j.ejpn.2011.08.007
[15] Rosati A, Ilvento L, Rizzi R, Doccini V, Leo MC, Pugi A, De Masi S, Guerrini R. Long-term efficacy of add-on lacosamide treatment in children and adolescents with refractory epilepsies: A single-center observational study. *Epilepsia*. 2018; 59(5): 1004-10. doi:10.1111/epi.14071
[16] Arkilo D, Gustafson M, Ritter FJ. Clinical experience of intravenous lacosamide in infants and young children. *European journal of paediatric neurology : EJPN : official journal of the European Paediatric Neurology Society*. 2016; 20(2): 212-7. doi:10.1016/j.ejpn.2015.12.013
[17] Yorns WR, Jr., Khurana DS, Carvalho KS, Hardison HH, Legido A, Valencia I. Efficacy of lacosamide as adjunctive therapy in children with refractory epilepsy. *Journal of child neurology*. 2014; 29(1): 23-7. doi:10.1177/0883073812462887
[18] Toupin JF, Lortie A, Major P, Diadori P, Vanasse M, Rossignol E, D'Anjou G, Perreault S, Larbrisseau A, Carmant L, et al. Efficacy and safety of lacosamide as an adjunctive therapy for refractory focal epilepsy in paediatric patients: a retrospective single-centre study. *Epileptic disorders : international epilepsy journal with videotape*. 2015; 17(4): 436-43. doi:10.1684/epd.2015.0782
[19] Pasha I, Kamate M, Didagi SK. Efficacy and tolerability of lacosamide as an adjunctive therapy in children with refractory partial epilepsy. *Pediatric neurology*. 2014; 51(4): 509-14. doi:10.1016/j.pediatrneurol.2014.07.004
[20] Farkas V, Steinborn B, Flamini JR, Zhang Y, Yuen N, Borghs S, Bozorg A, Daniels T, Martin P, Carney HC, et al. Efficacy and tolerability of adjunctive lacosamide in pediatric patients with focal seizures. *Neurology*. 2019; 93(12): e1212-e26. doi:10.1212/wnl.0000000000008126
[21] Grosso S, Parisi P, Spalice A, Verrotti A, Balestri P. Efficacy and safety of lacosamide in infants and young children with refractory focal epilepsy. *European journal of paediatric neurology: EJPN: official journal of the European Paediatric Neurology Society*. 2014; 18(1): 55-9. doi:10.1016/j.ejpn.2013.08.006
[22] Kim JS, Kim H, Lim BC, Chae JH, Choi J, Kim KJ, Hwang YS, Hwang H. Lacosamide as an adjunctive therapy in pediatric patients with refractory focal epilepsy. *Brain & development*. 2014;36(6):510-5. doi:10.1016/j.braindev.2013.07.003
[23] Miskin C, Khurana DS, Valencia I, Legido A, Hasbani DM, Carvalho KS. Efficacy and Tolerability of Lacosamide in the Treatment of Children With Refractory Generalized Epilepsy. *Journal of child neurology*. 2016; 31(7): 925-8. doi:10.1177/0883073816630084

[24] Rastogi RG, Ng YT. Lacosamide in refractory mixed pediatric epilepsy: a prospective add-on study. *Journal of child neurology*. 2012; 27(4): 492-5. doi:10.1177/0883073812436741
[25] Guilhoto LM, Loddenkemper T, Gooty VD, Rotenberg A, Takeoka M, Duffy FH, Coulter D, Urion D, Bourgeois BF, Kothare SV. Experience with lacosamide in a series of children with drug-resistant focal epilepsy. *Pediatric neurology*. 2011; 44(6): 414-9. doi:10.1016/j.pediatrneurol.2010.12.003
[26] Gulati P, Cannell P, Ghia T, Bint L, Walsh P, Ghosh S, Nagarajan L. Lacosamide as adjunctive therapy in treatment-resistant epilepsy in childhood. *J Paediatr Child Health*. 2015; 51(8): 794-7. doi:10.1111/jpc.12850
[27] Casas-Fernández C, Martínez-Bermejo A, Rufo-Campos M, Smeyers-Durá P, Herranz-Fernández JL, Ibáñez-Micó S, Campistol-Plana J, Alarcón-Martínez H, Campos-Castelló J. Efficacy and tolerability of lacosamide in the concomitant treatment of 130 patients under 16 years of age with refractory epilepsy: a prospective, open-label, observational, multicenter study in Spain. *Drugs in R&D*. 2012; 12(4): 187-97. doi:10.2165/11636260-000000000-00000
[28] Grosso S, Zamponi N, Bartocci A, Cesaroni E, Cappanera S, Di Bartolo R, Balestri P. Lacosamide in children with refractory status epilepticus. A multicenter Italian experience. *European journal of paediatric neurology : EJPN : official journal of the European Paediatric Neurology Society*. 2014; 18(5): 604-8. doi:10.1016/j.ejpn.2014.04.013
[29] Gavatha M, Ioannou I, Papavasiliou AS. Efficacy and tolerability of oral lacosamide as adjunctive therapy in pediatric patients with pharmacoresistant focal epilepsy. *Epilepsy & behavior : E&B*. 2011; 20(4): 691-3. doi:10.1016/j.yebeh.2011.02.005
[30] Shervin Badv R, Memarian S, Moghaddam HF, Gharib B, Yarali B, Alizadeh H, Heidari M. Efficacy of potassium bromide (As an out-of-date drug) in epilepsia partialis continua: A brief report. *Iranian journal of pediatrics*. 2016; 26(6).
[31] Afra P, Adamolekun B. Lacosamide treatment of juvenile myoclonic epilepsy. *Seizure*. 2012; 21(3): 202-4. doi:10.1016/j.seizure.2011.12.010
[32] Buck ML, Goodkin HP. Use of lacosamide in children with refractory epilepsy. *The journal of pediatric pharmacology and therapeutics : JPPT : the official journal of PPAG*. 2012; 17(3): 211-9. doi:10.5863/1551-6776-17.3.211
[33] Poddar K, Sharma R, Ng YT. Intravenous Lacosamide in Pediatric Status Epilepticus: An Open-Label Efficacy and Safety Study. *Pediatric neurology*. 2016; 61: 83-6. doi:10.1016/j.pediatrneurol.2016.03.021
[34] Sanmartí-Vilaplana F, Díaz-Gómez A. The effectiveness and safety of lacosamide in children with epilepsy in a clinical practice setting. *Epilepsy & behavior: E&B*. 2018;79:130-7. doi:10.1016/j.yebeh.2017.11.024
[35] Wei SH, Lee WT. Comorbidity of childhood epilepsy. *Journal of the Formosan Medical Association = Taiwanyizhi*. 2015; 114(11): 1031-8. doi:10.1016/j.jfma.2015.07.015
[36] Beydoun A, D'Souza J, Hebert D, Doty P. Lacosamide: pharmacology, mechanisms of action and pooled efficacy and safety data in partial-onset seizures. *Expert review of neurotherapeutics*. 2009; 9(1): 33-42. doi:10.1586/14737175.9.1.33
[37] Rogawski MA, Tofighy A, White HS, Matagne A, Wolff C. Current understanding of the mechanism of action of the antiepileptic drug lacosamide. *Epilepsy research*. 2015; 110: 189-205. doi:10.1016/j.eplepsyres.2014.11.021