fortune Journals

Research Article

JOURNAL OF CANCER SCIENCE AND CLINICAL THERAPEUTICS

ISSN: 2637-5079

Direct Medical Costs in the Care of Pediatric Patients with Nonsyndromatic Epilepsy: Using Levetiracetam and Valproic Acid

Diana Leticia Pérez-Lozano[1,2], Liliana Carmona-Aparicio[2,3,4*], Marcos Torres-Vázquez[5], Silvestre García-de la Puente[6], Miriam Palma-Barona[3], Perla Michelle Martínez[7], Tarsila Elizabeth Juárez-Zepeda[3], Elvia Coballase-Urrutia[3], Liliana Rivera-Espinosa[8], Hortencia Montesinos-Correa[9], Aristides III Sampieri[4], Matilde Ruíz-García[10]

Abstract

Purpose: To determine the direct medical costs associated with the medical care of pediatric patients with nonsyndromatic epilepsy treated with valproic acid (VPA) and levericetam (LEV).

Patients and methods: An observational, retrospective and longitudinal study. The costs generated by medical care for the patients receiving VPA and LEV treatment were obtained by microcosting approach, this was undertaken combining utilization data with unit costs to estimate total cost from the management of children with epilepsy during the study period (10 years).

Results: 1362 patients who met the diagnostic criteria for nonsyndromatic epilepsy, 46% (n=184) were prescribed VPA monotherapy, and 25% (n=100) were prescribed LEV, followed by other anti-seizure medications (ASM) less frequently. Only 167 patients had complete data and continuous treatment for 6 months with appropriate follow up and were included in the costing analysis, where the total annual cost of care of pediatric patient with epilepsy non syndromatic was $292,008.00 USD. For patients treated with VPA, the direct medical cost was $36,405.00 USD for medical consultations, $58,660.00 USD for laboratory and neuroimaging studies, $26,728.00 USD for hospitalization and $20,704.00 USD for medication, while for patients treated with LEV, the total direct medical cost was $15,499.00 USD for medical consultations, $63,759.00 USD for laboratory and neuroimaging studies, $31,196.00 USD for hospitalization costs and $39,057.00 USD for medication.

Conclusion: Patients treated with VPA had a direct medical cost of $142,497.00 USD (mean, $1307.31), while those treated with LEV had a total direct medical cost of $149,511.00 USD (mean $2577.77).

Keywords: Epilepsy; Direct medical cost; Pharmacoeconomics; Valproic acid; and Levetiracetam.

Introduction

Epilepsy is one of the most common chronic neurological diseases [1], with a prevalence of 6.38 per 1,000 persons [2], an incidence of 67.77 per 100,000 persons, and a childhood incidence rate of 1.8% worldwide [3, 4]. Approximately 80% of affected people live in low- and middle-income countries, and epilepsy is considered a public health problem [4]. Epilepsy is characterized by an abnormal increase in the electrical activity of cortical neurons that manifests as recurrent, spontaneous, excessive and unpredictable

Affiliation:

[1]Degree in General and Community Medicine, University of Health, UNISA Campus Santa Fe, Mexico City, Mexico.

[2]Postgraduate in Medical Sciences, Clinical Research, UNAM, Mexico City, Mexico

[3]Laboratory of Neuroscience II, National Institute of Pediatrics, Mexico City, Mexico

[4]Faculty of Sciences, UNAM, Mexico City, Mexico

[5]Technical Control Unit of the National Electoral Institute, Mexico City, Mexico

[6]Department of Research Methodology, National Institute of Pediatrics, Mexico City, Mexico

[7]School of Pharmacy, The University of Texas at El Paso, Texas, USA.

[8]Laboratory of Pharmacology, National Institute of Pediatrics, Mexico City, Mexico

[9]Endocrinology Service, National Institute of Pediatrics, Mexico City, Mexico

[10]Neurology Service, National Institute of Pediatrics, Mexico City, Mexico

***Corresponding author:**
Liliana Carmona-Aparicio, PhD. Faculty of Sciences, UNAM, Mexico City, Mexico, and Laboratory of Neuroscience II, National Institute of Pediatrics, Ministry of Health, Mexico City, Mexico.

Citation: Diana Leticia Pérez-Lozano, Liliana Carmona-Aparicio, Marcos Torres-Vázquez, Silvestre García-de la Puente, Miriam Palma-Barona3, Perla Michelle Martínez, Tarsila Elizabeth Juárez-Zepeda, Elvia Coballase-Urrutia, Liliana Rivera-Espinosa, Hortencia Montesinos-Correa, Aristides III Sampieri, Matilde Ruíz-García. Direct Medical Costs in the Care of Pediatric Patients with Nonsyndromatic Epilepsy: Using Levetiracetam and Valproic Acid. Journal of Cancer Science and Clinical Therapeutics. 8 (2024): 126-134.

Received: May 09, 2024
Accepted: May 24, 2024
Published: June 11, 2024

Pérez-Lozano DL, et al., J Cancer Sci Clin Ther 2024
DOI:10.26502/jcsct.5079233

seizures [5]. In the initial treatment, the specific type of seizure suffered by the child should be determined, and if possible, a determination of epilepsy syndrome should be made [6]. The WHO [4] recommends phenobarbital as the treatment of choice for partial and tonic–clonic seizures in countries with limited resources [7]. In Mexico, clinical practice guidelines recommend the use of valproic acid (VPA), carbamazepine (CBZ) and topiramate (TPM) for focal seizures and VPA, TPM and lamotrigine (LTG) for generalized seizures in pediatric patients [8], with levetiracetam (LEV), CBZ, phenytoin (DFH), phenobarbital (PB) and vigabatrin (VGB) being other appropriate treatments for epilepsy. In addition to pharmacological treatment, social factors, as well as the personal, occupational and academic development of patients with epilepsy, are essential for improving their quality of life. At the National Institute of Pediatrics (NIP, Mexico City), children with nonsyndromatic epilepsy (principally focal epilepsy) are frequently treated with VPA (both mono- and combined therapy), followed by LEV [9]. In 2007, spending on medicines in Mexico represented 24% of the total health expenditure (1.4% of gross domestic product). Most of this expense (75%) is out-of-pocket. The Mexican Social Security Institute concentrates 47.9% of public spending on medicines, followed by institutions that serve the uninsured population, with 26.8% [10]. On the other hand, studies that report direct and indirect medical costs, as well as cost-effectiveness analysis, are scarce both in Mexico and in other Latin American countries, and these studies are more limited when studying specific diseases such as epilepsy; in particular, in Spain, they have reported cost-effectiveness 'type' studies in hypothetical cohorts (1,000 patients), with an annual medical cost of $184,274.00 USD in refractory focal epilepsy, indicating that pregabalin (PGB, third generation ASM) provides better cost-effectiveness than LEV for additional seizure-free days and quality-adjusted life years gained [11]. García-Contreras et al. (2006) [12] reported the direct medical cost of refractory focal epilepsy in patients >12 years of age with more than two anti-seizure medications (ASMs) and a one-year follow-up and concluded that the annual health cost of 72 patients was $190,486.00 USD (2,645.65 USD by patient) [12]. The application of the knowledge and techniques of economic evaluation in the pharmacological field allows focusing the analysis on the resolution of problems posed by an adequate prescription, from an effectiveness point of view, as well as in attaining efficiency at a reasonable cost. This study aimed to determine the direct medical costs associated with the medical care of pediatric patients with nonsyndromatic epilepsy treated with VPA and LEV (2008-2018).

Materials and Methods

Study population and variables

The cost evaluations were carried out by obtaining information on the study variables from the clinical records of patients with a diagnosis of epilepsy (International Classification of Diseases-10 of G409), of nonsyndromatic type, who received care in the epilepsy clinic of the neurology service of the NIP, with complete adherence to treatment with ASM in the monotherapy regimen and attendance at medical check-up appointments scheduled by the treating physician within a period of 6 months. All procedures performed for this observational, retrospective, longitudinal and analytical study were carried out in accordance with the Declaration of Helsinki and of the General Health Law on Research for Health in Mexico and were performed following Protocol-NIP 059/2018, approved by the Research Board of the NIP (IRB00008065) and the Research Ethics Committee (IRB00008064) registered at the Office for Human Research Protection of the National Institute of Health (NIH).

Patient selection

Patients diagnosed with nonsyndromatic epilepsy, with ASM (period of a minimum of six months) and attended the neurology clinic of the NIP epilepsy clinic were included. Patients who presented any irregularity regarding their clinical records, incomplete treatment, unspecified dose and unrecorded seizure control were excluded.

The quantitative variables were age, obtained from the medical records at the time of the study and quantified in years; number of consultations; number of hospitalizations; number of laboratories performed by patients and reported in the clinical records; and indicated dosage of the ASM from the initial visit to the final visit of the study year. The socioeconomic level: Status referring to socioeconomic income, indicated by a study carried out by social work. the collection percentages according to the assigned level; Therefore, in the NIP they are applied as follows: level 1N (3%), level 2N (8%), level 3N (23%), level 4N (50%), level 5N (75%) and level 6N (100%). The dichotomous variable was biological sex, which was established in the clinical history, and the qualitative variables were etiology, type of seizure and control of epilepsy, which were reported in the clinical history. The degree of control of seizures was considered absolute: absence of seizures; partial: reduction of seizures to 50%; without control: without changes in the number of seizures, in a monthly follow-up, with use of a diary of the primary caregiver. These variables were used to determine the clinical profile of the patients.

Microcosting

Direct medical costs were determined during an annual period, to obtain the average annual cost, the study years ranged from January 1, 2008 to December 31, 2018. The specific variables used to determine the costs were a) medical consultations costs, referring to the type (such as neurology, cardiology, anesthesiology to perform magnetic

Citation: Diana Leticia Pérez-Lozano, Liliana Carmona-Aparicio, Marcos Torres-Vázquez, Silvestre García-de la Puente, Miriam Palma-Barona3, Perla Michelle Martínez, Tarsila Elizabeth Juárez-Zepeda, Elvia Coballase-Urrutia, Liliana Rivera-Espinosa, Hortencia Montesinos-Correa, Aristides III Sampieri, Matilde Ruíz-García. Direct Medical Costs in the Care of Pediatric Patients with Nonsyndromatic Epilepsy: Using Levetiracetam and Valproic Acid. Journal of Cancer Science and Clinical Therapeutics 8 (2024): 000-000. 8 (2024): 126-134.

Pérez-Lozano DL, et al., J Cancer Sci Clin Ther 2024
DOI:10.26502/jcsct.5079233

resonance imaging, neurosurgery, rehabilitation, infectology, genetics, nutrition, hematology, audiology, ophthalmology, gastroenterology, phoniatrics, pulmonology, human communication, urology and stomatology services) and frequency of these; b) costs of laboratory (determination of uric acid, ammonium, colesterol, creatinine, urinalysis, Folates, gasometry, globulins, glucose, glycosylated hemoglobin, vitamin B12 levels, thyroid profile, prealbumin, total proteins, triglycerides and others) and neuroimaging studies (electroencephalogram, magnetic resonance and computerized axial tomography), referring to the type and frequency of these; c) hospitalization costs, referring to the sum of patient-bed days, adding the type of diet, the specialized procedures performed and the additional medication to the ASM; and d) medication costs, referring to the quantities of ASM in grammage according to what is required by the patient's weight and the treatment period. Direct medical costs were calculated by the microcosting method, which is understood as the detailed estimate of the use of each component or resource, as well as its frequency, which is subsequently used with the price of each of these components to estimate the cost of an intervention in the management of the disease. This study analyzed the direct medical costs of medical care for pediatric patients with nonsyndromatic epilepsy treated with VPA and LEV during a study year using the microcosting method.

Unit supply costs

The costs were obtained based on the NIP Cost Tabulator (source of unit costs established by the institute), which reports the unit costs used in medical care within the institution, given that this evaluation has an institutional perspective. The economic value was calculated using data obtained from the NIP in Mexico City, a quota tab corresponding to the last year of study, as managed in the Planning Direction of this Institute. The price of ASM were taken from the drug price list granted by the Procurement Department and Inventories of the NIP in Mexico City.

Statistical analysis: Estimation of Utilization and Unit Costs

The study was carried out through an analysis of direct medical costs, with a time of one year, by the microcosting method, in which variable costs were calculated for each of the ASM. Based on the NIP Cost Tabulator, within the prices of the therapeutic approach of the patients, a variable was assigned for each cost, comprising the ASM, laboratory and neuroimaging studies, and hospitalization (drugs, supplies, procedures and professional fees). Labor was assigned as professional fees according to the number of consultations that the patient had within the institute. The price of the ASM was calculated annually based on the weight of the patient at the time of the study and the indication from the Neurology Service. Initially, the subtotals corresponding to the cost of hospitalization, medical consultations, medications, laboratory and neuroimaging studies were obtained from individual files. Later, the total annual cost was calculated, as was the average total cost of epilepsy in the NIP. The analysis of hospitalization costs, medical consultation costs, medication costs and laboratory and neuroimaging studies costs was carried out by individual clinical records, and the totals corresponding to the four mentioned items were obtained from the sum of the patients treated with ASM. Subsequently, the total annual cost of medical care for patients with nonsyndromatic epilepsy was calculated, and the average cost per patient was obtained. Finally, the distribution of the data was determined, and the statistical program SPSS version 21 was used for the statistical analysis. The Kolmogorov–Smirnov normality test was performed depending on the number of individuals per variable to determine the type of distribution. Descriptive results are reported as the range and percentage. No sensitivity analysis was performed.

Results

From January 2008 to December 2018, 1362 patients from the study population were reviewed, and 682 had a diagnosis of epilepsy, of whom 605 were diagnosed with nonsyndromatic epilepsy; of these 400 patients, only ASM (monotherapy) was prescribed. The frequencies of all ASM used in monotherapy were as follows: VPA, 46% (n=184); LEV, 25% (n=100); oxcarbazepine (OXC), 11.5% (n=46); CBZ, 5% (n=20); DFH, 4.75% (n=19); PB, 3.7% (n=15); TPM, 2.5% (n=10); LTG, 0.7% (n=3); and VGB, 0.7% (n=3). The two most prescribed ASM were obtained; however, only 167 met the criteria for microcosting analysis (VPA, n=109; LEV, n=58), from which the statistical analysis for this study was performed. Of the population studied, 56.3% (n=94) were male and 43.7% (n=73) were female, with an average age of 2.52 years. Regarding the socioeconomic level of NIP health users, the first three strata represented 97.6%. The pathological personal antecedents were prenatal (10.8%, n=18), perinatal (12.6%, n=21), postnatal (18%, n=30), prenatal and postnatal (1.2%, n=2), and other background (2.4%, 4) (Table 1). Finally, the frequencies of medical consultations and laboratory and neuroimaging studies are described in Table 2.

According to the analysis of bivariate frequencies for anti-seizure medication pharmacological treatment and crisis control variables, treatment with LEV presented a greater percentage of absolute control (77.5%, n= 45), treatment with VPA presented a percentage of absolute control (76.1%, n=83%) and partial control (22.9%, n=25%), and both drugs had lower frequencies of no control, LEV (3.4%, n=2), and VPA (0.91%, n=1) (Figure 1).

For 100% of the studied patients (n=167), the annual costs generated by nonsyndromatic epilepsy were determined by

Citation: Diana Leticia Pérez-Lozano, Liliana Carmona-Aparicio, Marcos Torres-Vázquez, Silvestre García-de la Puente, Miriam Palma-Barona3, Perla Michelle Martínez, Tarsila Elizabeth Juárez-Zepeda, Elvia Coballase-Urrutia, Liliana Rivera-Espinosa, Hortencia Montesinos-Correa, Aristides III Sampieri, Matilde Ruíz-García. Direct Medical Costs in the Care of Pediatric Patients with Nonsyndromatic Epilepsy: Using Levetiracetam and Valproic Acid. Journal of Cancer Science and Clinical Therapeutics 8 (2024): 000-000. 8 (2024): 126-134.

Pérez-Lozano DL, et al., J Cancer Sci Clin Ther 2024
DOI:10.26502/jcsct.5079233

Table 1: Distribution of the clinical characteristics of the microcosting population (LEV, VPA) in patients with nonsyndromic epilepsy (n=167).

	VPA (n=109, 65%)	LEV (n=58, 35%)	Total (n %)
Sex			
Male	58 (34%)	36 (21.5%)	94 (56.3%)
Diagnosis age	2.30 (+/-0.29)	2.91 (+/0.52)	2.52 (+/-0.17)
Socioeconomic level			
1N	45 (26.9%)	11 (6.5%)	56 (33.5%)
1X	5 (2.9%)	7 (4.1%)	12 (7.2%)
2N	46 (27.5%)	27 (16.1%)	73 (43.7%)
3N	12 (7.1%)	10 (5.9%)	22 (13.2%)
Seizures control			
Absolute	83 (49.7%)	45 (26.9%)	128 (76.6%)
Partial	25 (14.9%)	11 (6.5%)	36 (21.5%)
No control	1 (0.5%)	2 (2%)	3 (1.8%)
Type of seizures			
Focal	72 (43.1%)	39 (23.3%)	112 (67.1%)
Generalized	17 (10.1%)	9 (5.3%)	26 (15.6%)
Secondary Generalized Focal	19 (11.3%)	8 (4.7%)	27 (16.2%)
Not specified	1 (0.5%)	1 (0.5%)	2 (1.1%)
Etiology			
Structural-metabolic	59 (35.3%)	41 (24.5%)	100 (59.9%)
Unknown	22 (13.1 %)	8 (4.7%)	30 (18.0%)
Genetics	14 (8.3%)	5 (2.9%)	19 (11.4%)
Not specified	14 (8.3%)	4 (2.3%)	18(10.8%)
Psychomotor development			
Normal	44 (26.3%)	19 (11.3%)	63 (37.7%)
Abnormal	59 (35.3%)	37 (22.1%)	96 (57.5%)
Not specified	6 (3.5%)	2 (1.1%)	8 (4.8%)

Notes: Socioeconomic level, status referring to socioeconomic income, indicated by a study carried out by social work.

the microcosting method, and a total for the two drugs of $292,008.00 USD was obtained during the studied period. The total cost of medical consultations was $51,904.00 USD, the hospitalization cost reached $57,924.00 USD, and the annual cost per medication was $59,761.00 USD. Of the four main costs reported, the highest was the cost of laboratories and neuroimaging studies, which amounted to $122,419.00 USD. For patients who used VPA as a base drug (65.3%) spent $58,660.00 USD (mean, $538.16) in laboratory and neuroimaging studies, with $36,405.00 USD (mean, $333.99) in medical consultations and $26,728.00 USD (mean, $245.21) in hospitalization. The cost of VPA as a drug was $20,704.00 USD (mean, $189.95). In total, this medicine generated $142,497.00 USD (mean per patient, $1307.31) for this pathology during the study period. The patients treated with LEV (34.7%) spent $15,499.00 USD (mean, $267.22) in medical consultations, $31,196.00 USD (mean, $537.86) in hospitalization costs, and $63,759.00 USD (mean, $1,099.29) in laboratory and neuroimaging studies. The cost of the drug was $39,057.00 USD (mean, $673.40). Therefore, for patients who used LEV treatment incurred an expense of $149.511.00 USD (mean per patient, $2577.77).

Citation: Diana Leticia Pérez-Lozano, Liliana Carmona-Aparicio, Marcos Torres-Vázquez, Silvestre García-de la Puente, Miriam Palma-Barona3, Perla Michelle Martínez, Tarsila Elizabeth Juárez-Zepeda, Elvia Coballase-Urrutia, Liliana Rivera-Espinosa, Hortencia Montesinos-Correa, Aristides III Sampieri, Matilde Ruíz-García. Direct Medical Costs in the Care of Pediatric Patients with Nonsyndromatic Epilepsy: Using Levetiracetam and Valproic Acid. Journal of Cancer Science and Clinical Therapeutics 8 (2024): 000-000. 8 (2024): 126-134.

Pérez-Lozano DL, et al., J Cancer Sci Clin Ther 2024
DOI:10.26502/jcsct.5079233

Table 2: Frequency of the main microcosting per year of medical consultations, hospitalizations and studies of the study population (LEV, VPA) in patients with nonsyndromic epilepsy (n=167).

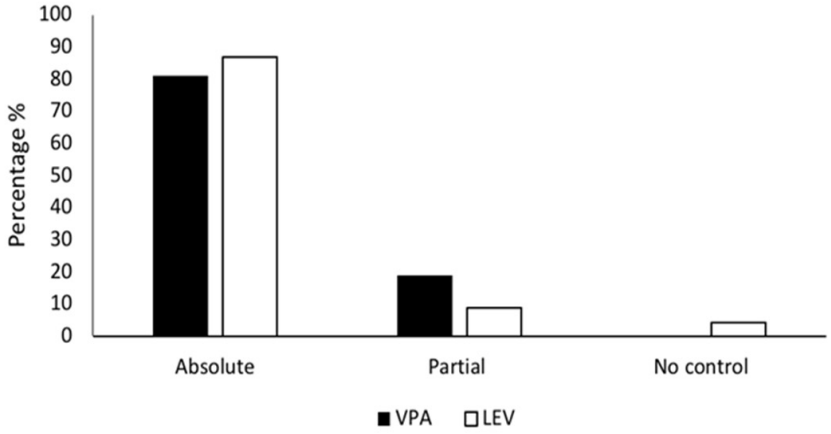
Main drug	**VPA (n=109)**	**LEV (n=58)**	**TOTAL**
Medical Consultations			
Number of Consultations	117	116	233
Neurology	52	55	107
Cardiology	1	1	2
Anesthesiology to perform Magnetic Resonance Imaging	1	2	3
Magnetic Resonance Imaging	4	4	8
Neurosurgery	1	2	3
Rehabilitation	10	12	23
Infectology	5	5	10
Genetics	5	5	10
Nutrition	4	4	8
Hematology	1	1	2
Audiology	7	4	11
Ophthalmology	6	4	10
Gastroenterology	8	4	14
Phoniatrics	1	3	4
Pulmonology	2	1	3
Human Communication	4	4	8
Urology	1	1	2
Stomatology	4	4	8
Prehospitalization (Emergency)			
Prehospital emergency number **(no pernota)** (spend the night) **(no pernota)** (spend the night)	75	21	96
Hospitalization			
Hospitalization Number	195	195	390
(Not spend the nigth)	270	216	486
Laboratory studies	1049	625	1674
Neuroimaging studies			
Number of Electroencephalograms	50	50	100
Magnetic Resonance Number	15	15	30
Simple CAT Number	9	9	18
CAT number simple and contrast	5	11	16

Notes: Valproic Acid (VPA), Levetiracetam (LEV), Computed axial tomography (CAT)

Citation: Diana Leticia Pérez-Lozano, Liliana Carmona-Aparicio, Marcos Torres-Vázquez, Silvestre García-de la Puente, Miriam Palma-Barona3, Perla Michelle Martínez, Tarsila Elizabeth Juárez-Zepeda, Elvia Coballase-Urrutia, Liliana Rivera-Espinosa, Hortencia Montesinos-Correa, Aristides III Sampieri, Matilde Ruíz-García. Direct Medical Costs in the Care of Pediatric Patients with Nonsyndromatic Epilepsy: Using Levetiracetam and Valproic Acid. Journal of Cancer Science and Clinical Therapeutics 8 (2024): 000-000. 8 (2024): 126-134.

Pérez-Lozano DL, et al., J Cancer Sci Clin Ther 2024
DOI:10.26502/jcsct.5079233

Figure 1: Seizures control vs drug treatment (VPA, LEV).



Notes: Patients with nonsyndromic epilepsy during the period from January 2008 to December 2018 (n=167). The percentages of seizure control, absolute, partial and no control were obtained based on the number of cases obtained by each ASM.

Table 3: Annual costs (mean) derivate of the attention of patients with nonsyndromic epilepsy, during the period of study, 2008-2018.

Principal	Medical consultations costs	Cost of laboratories and neuroimaging studies	Hospitalization cost	Medication costs	Total
ASMs	**Mean**	**Mean**	**Mean**	**Mean**	**Mean**
	(IC 95%)	**(IC 95%)**	**(IC 95%)**	**(IC 95%)**	**(IC 95%)**
VPA	$333.99	$538.16	$245.21	$189.94	$1307.31
(n=109)	(213.18-454.79)	(431.00-645.31)	(119.30-371.12)	(166.96-212.93)	(1037.08-1577.54)
LEV	$267.22	$1099.29	$537.86	$673.40	$2577.77
(n=58)	(212.50-321.93)	(805.46-1393.11)	(276.32-799.38)	(466.88-879.91)	(2095.05-3060.48)

Notes: Valproic Acid (VPA), Levetiracetam (LEV)

Discussion

The study population had a wide age distribution. The mean age of the study population was 2.52 years (+/-0.17), with a mean age of 2.30 years (+/-0.29) in the group of patients treated with VPA and a mean age of 2.91 years (+/-0.29) in the group of patients treated with LEV (+/-0.52), which coincided with the frequency of presentation of the convulsive phenomenon in the first year of life [1, 13-15]. A male predominance was found in the population (56.3%, n=94), which matches that reported since males are generally predominantly affected [13, 16]. Therefore, the population studied complied with the characteristics of an open population; considering that the NIP is a third-level hospital and consequently receives medical care, more specific cases came to our consultation [17]. Deficiencies or intermittency in the provision of ASMs by health services or lack of means for the patients themselves to pay for their treatment may arise due to the economic situation of the country. It is estimated that only up to 20% of the population in Latin America has private health insurance, and most of them do not include the cost of medicines [18-19]. In cases where the cost of the drug is borne by the NIP and not by the patient, a discount percentage is maintained depending on the socioeconomic classification, which ranges from 97.5% for the 1 N level to 0.0% for the 6 N level (Dates provided by NIP, 2018). It is important to highlight that in the distribution by socioeconomic level, the first three strata represented 97.6%. On average, a patient must pay $20,704.00 USD per year for medication in the case of VPA and $39,057.00 USD for LEV. In addition, there is a difference in the price between first-generation ASM (VPA, CBZ, DFH, PB) and newer ASM, which implies that they are becoming up to 100 times more expensive [19]. It is worth mentioning that the costs presented in this study are the first reported for children with nonsyndromatic epilepsy receiving monotherapy, where the amounts shown are expenses totally absorbed by the institution. With respect to the frequencies and costs reported in this study, VPA was the most widely used antiepileptic drug for monotherapy and polytherapy, which occurred between 2008 and 2018 (605 patients); however, by reducing the population for economic analysis (167 patients), LEV had a greater frequency, at 16.5%. LEV has broad-spectrum activity and minimal interactions with other medications; hence, it has become a common option for the first-line treatment of epilepsy in early life, although other medications are equally reasonable, and the option must be individualized [20]. However, these data suggest a change in the trend of

Citation: Diana Leticia Pérez-Lozano, Liliana Carmona-Aparicio, Marcos Torres-Vázquez, Silvestre García-de la Puente, Miriam Palma-Barona3, Perla Michelle Martínez, Tarsila Elizabeth Juárez-Zepeda, Elvia Coballase-Urrutia, Liliana Rivera-Espinosa, Hortencia Montesinos-Correa, Aristides III Sampieri, Matilde Ruíz-García. Direct Medical Costs in the Care of Pediatric Patients with Nonsyndromatic Epilepsy: Using Levetiracetam and Valproic Acid. Journal of Cancer Science and Clinical Therapeutics 8 (2024): 000-000. 8 (2024): 126-134.

Pérez-Lozano DL, et al., J Cancer Sci Clin Ther 2024
DOI:10.26502/jcsct.5079233

prescription regimens due to the use of new ASM, which have fewer side effects and have good availability and efficacy in the last 10 years [21]; nevertheless, VPA is described as the most commonly used ASM, followed by CBZ [9]. When analyzing the costs of epilepsy, the current trend tends to assess the so-called direct medical costs. The NIP reported a total amount of $292,008.00 USD from January 1, 2008, to December 31, 2018. By subdividing the total cost, we can see that $59,761.00 USD corresponds to the drug, while the cost of medical consultations was $51,904.00 USD, and the cost per hospitalization reached $57,924.00 USD. Of the four main costs reported in this study, the highest (nearly half of the total cost) was the cost of laboratories and neuroimaging studies, which amounted to $122,419.00 USD. The treatment of patients treated with VPA (65.2%) generated a cost of $58,660.00 USD in laboratories and neuroimaging studies, $36,405.00 USD in medical consultations and $26,728.00 USD in hospitalizations due to uncontrolled seizures. A total of 43.5% of these patients were hospitalized, and 76.1% achieved absolute crisis control. The annual cost of buying this drug was $20,704.00 USD; in total, this drug generated $142,497.00 USD for the treatment of children with nonsyndromatic epilepsy. Patients using LEV as the main ASM (34.7%) spent $31,196.00 USD, $63,759.00 USD and $15,499.00 USD, on hospitalization costs, laboratory and neuroimaging studies and consultations, respectively. The annual cost of LEV was $39,057.00 USD. Therefore, LEV treatment produced an expense of $149,511.00 USD, which resulted in a more expensive alternative considering that the percentage of seizure control was only 77.5% and the hospitalization percentage was 47.4%. There is no doubt that the increase in this therapeutic alternative lies in the cost of the drug, since that is where the maximum increase is observed compared to that of VPA. Based on this, there was a difference in the average cost per patient of $1,271.00 USD between the alternatives. Hence, the results of the model showed that VPA obtained more favorable cost values than LEV in the pharmacological treatment of children with nonsyndromatic epilepsy.

As reported in the literature, LEV is an ASM with good efficacy and a good safety profile, and it is licensed as monotherapy for adults and children over 16 years of age with focal seizures, with or without secondary generalization. However, it is increasingly used off-label in younger children [22]. The LEV prescription rate increased by 10% within 8 years after 2000 in the United Kingdom and 8% within 10 years in Wales. In Taiwan, the LEV prescription rate increased from 0% in 2003 to 18% in 2007 [23]. In a systematic review, LEV in 30 trials of complementary therapy in the pediatric population presented a crisis reduction between the reference and treatment periods that ranged from 10.5% to 31.2% in children [24]. On the other hand, in a randomized, double-blind trial conducted in children with refractory focal seizures (198 patients), the average percentage of crisis reduction was 43.8% in children treated with LEV as adjunct therapy, compared to 23.3% in the placebo-treated group [25]. In a randomized, placebo-controlled, double-blind, multicenter trial with 38 patients who were enrolled to assess the efficacy of LEV in children and adolescents with epilepsy who were recently diagnosed with childhood and juvenile absence seizures, 23 patients (7%) ceased having absence seizures. In the placebo group, 4.8% were free of seizures; nonetheless, the difference was not statistically significant [26]. In an open study of 20 patients, VPA resulted in a greater than 50% reduction in the frequency of epileptic seizures, and in 3 patients, VPA halted seizures [27]. In a randomized, open-label parallel-group design, 38 children were included, 19 with VPA and 19 with LTG treatment. In a follow-up of 12 months, 13 patients who were taking VPA (68.4%) and 10 who were taking LTG (52.6) were seizure free. The side effects reported were mild and transient and were recorded in 2 patients with VPA-treatment (10.6%) and in 6 with LTG-treatment (31.8%) [28]. According to the evidence presented, the efficacy measures of LEV were consistent, with a crisis reduction of 27.1% (0.27) and efficacy intervals ranging from 10.5% to 43.8% in the 88 patients who were treated. In the case of VPA, efficacy intervals from 50% to 68.4% were recorded, an efficacy of 59.2% (0.59) within the population. A limitation of this study, is not having estimated the drop-out rate due to adverse drug reactions, which were considered within the study variables; however, the reported incidence was 1.1% (n = 2) (without indicating the type of reaction or its severity). Nevertheless, we do not know the impact that this would have had on the control of the seizures and on the quality of life of the patients. There could be a bias in the indication of ASM, since it is unknown under what criteria each doctor decided to prescribe one or another drug. It should be considered that LEV has a broad spectrum, which is why it is prescribed more commonly, and that in some cases patients with this medication present complications that may affect the effectiveness of this medication. It cannot be ruled out that the use of LEV is attributed to the patient having better economic means. The present study is not a controlled trial, so it has the limitation that direct comparisons between VPA and LEV are subject to bias considering that patient groups may differ in factors other than medications and other care received, which is why recommend conducting follow-up-controlled studies to further test these findings. Finally, as a general Limitation, the populations studied were patients of a third-level hospital, and therefore, the reported cases were more serious. and, it should be considered that both drugs have a broad spectrum and that VPA has been in use since the 1970s, unlike LEV, whose use began 20 years later; consequently, there is a greater variety of brands and prices for VPA, in addition to the fact that there is greater knowledge of the unwanted and adverse effects that occur when treating patients with this medication. It is worth mentioning that this study is based

Citation: Diana Leticia Pérez-Lozano, Liliana Carmona-Aparicio, Marcos Torres-Vázquez, Silvestre García-de la Puente, Miriam Palma-Barona3, Perla Michelle Martínez, Tarsila Elizabeth Juárez-Zepeda, Elvia Coballase-Urrutia, Liliana Rivera-Espinosa, Hortencia Montesinos-Correa, Aristides III Sampieri, Matilde Ruíz-García. Direct Medical Costs in the Care of Pediatric Patients with Nonsyndromatic Epilepsy: Using Levetiracetam and Valproic Acid. Journal of Cancer Science and Clinical Therapeutics 8 (2024): 000-000. 8 (2024): 126-134.

Pérez-Lozano DL, et al., J Cancer Sci Clin Ther 2024
DOI:10.26502/jcsct.5079233

on what is described in the population treated and that these variables, such as the variety of brands and prices, may influence the existence of a much cheaper presentation and can impact the direct medical cost. We must also consider that although we did not find this in this series, due to the age of the population studied, frequently, patients treated with VPA are subjected to frequent studies where plasma VPA levels, blood biometry and liver function tests are determined, and in adolescents treated with VPA, these patients may present more frequently with obesity, gastritis, thrombocytopenia and greater interactions with other medications. In addition, their side and toxic effects limit its use, especially in young women of reproductive age [29], and its participation in liver damage in Alpers-Huttenlocher disease [30, 31]. On the other hand, LEV has been associated with behavioral alterations [32], and the adverse effects and drug interactions that this medication can induce are still under study.

Finally, more exhaustive studies will have to be conducted to determine the effectiveness of VPA and LEV and to determine whether these ASM result in greater cost-effectiveness or a better quality of life for patients. Although the direct cost is important, as is the safety and efficacy profile, the therapeutic effectiveness of ASM must be ensured, considering that it has been reported that LEV is less effective than VPA and OXC in children and adolescents with epilepsy when administered as monotherapy [33].

Conclusion

The direct medical cost incurred by epilepsy care was $292,008.00 USD for children with nonsyndromatic epilepsy treated with LEV and VPA (n=167), where it was observed that LEV represented to average cost per patient of $2,578.00 USD (n=58) and VPA $1,307.00 USD (n=109). This partial economic evaluation can contribute to the updating of information and, in this way, provide evidence that can help health professionals, as well as the corresponding health institutions, improve the decision-making process to choose appropriate therapeutic treatment options within this population.

Acknowledgments

We thank Mr. Sergio Humberto Larios-Godínez and Dr. Noemi Cárdenas-Rodríguez for providing technical assistance.

Conflicts of interests

The all authors declare that they have no conflicts of interests.

Funding

We appreciate the support received from Protocol 059/2018, Program-E022 of the National Institute of Pediatrics (Ministry of Health, Mexico), and Scholarship No. 706968 (CONACyT, Mexico), which supported studies by Diana Leticia Pérez-Lozano of the Doctoral Program of the Medical, Dental and Health Sciences, Clinical Experimental Health Research, Clinical Pharmacology, UNAM, Mexico.

References

1. Beghi E. The epidemiology of epilepsy. Neuroepidemiology 54 (2020): 185-191.
2. Fiest KM, Sauro KM, Wiebe S, et al. Prevalence and incidence of epilepsy: a systematic review and meta-analysis of international studies. Neurology 88 (2017): 296-303. Erratum in: Neurology 89 (2017): 642.
3. Cruz-Alcalá LE, Vázquez-Castellanos JL. Prevalencia de algunas enfermedades neurológicas en la Ciudad de Tepatitlán, Jalisco, México. Rev Mex Neuroci 3 (2002): 71-76.
4. World Health Organization. Informe sobre la salud en el mundo: colaboremos por la salud. World Health Organization (2006).
5. Fisher RS, Acevedo C, Arzimanoglou A, et al. ILAE official report: a practical clinical definition of epilepsy. Epilepsia 55 (2014): 475-482.
6. Arya R, Glauser TA. Pharmacotherapy of focal epilepsy in children: a systematic review of approved agents. CNS Drugs 27 (2013): 273-286.
7. Perucca E. Treatment of epilepsy in developing countries. BMJ 334 (2007): 1175-1176.
8. Guía de Práctica Clínica, Diagnóstico y tratamiento de la primera crisis convulsiva en niñas, niños y adolescentes. Ciudad de México. Secretaría de Salud (2017).
9. Sánchez SO, Ruíz GM, Polanco MYC, et al. Perfil clínico y fármaco-terapéutico de la población con epilepsia parcial en edad pediátrica del Instituto Nacional de Pediatría. Acta Universitaria 24 (2014): 84-90.
10. Gómez DO, Sesma S, Becerril VM, et al. Sistema de Salud de México. [The health system of Mexico]. Salud Publica de Mexico 53 (2011): s220-s232.
11. Díaz S, Argumosa A, Horga de la Parte JF, et al. Análisis coste-efectividad del tratamiento de la epilepsia parcial refractaria: un modelo de simulación de pregabalina y levetiracetam [Analysis of the cost-effectiveness of treatment for refractory partial epilepsy: a simulation model for pregabalin and levetiracetam]. Revista de Neurologia 45 (2007): 460-467.
12. García-Contreras F, Constantino-Casas P, Castro-Ríos A, et al. Direct medical costs for partial refractory epilepsy in Mexico Archives Medical Research 37 (2006): 376-383.

Pérez-Lozano DL, et al., J Cancer Sci Clin Ther 2024
DOI:10.26502/jcsct.5079233

13. Ali A. Global Health: Epilepsy. Seminars in Neurology 38 (2018): 191-199.

14. Suástegui R, Gutiérrez J, Ramos R, et al. Características clínicas de la epilepsia de inicio tardío en México al principio del nuevo milenio: 455 casos [Clinical characteristics of the late-onset epilepsy in Mexico to the beginning of the new millennium: 455 cases]. Revista en Investigación Clinica 61 (2009): 354-363.

15. Kwan P, Arzimanoglou A, Berg AT, et al. Definition of drug resistant epilepsy: consensus proposal by the ad hoc Task Force of the ILAE Commission on Therapeutic Strategies. Epilepsia 51 (2010): 1069-1077. Erratum in: Epilepsia. 51 (2010): 1922.

16. Berg AT, Berkovic SF, Brodie MJ, et al. Revised terminology and concepts for organization of seizures and epilepsies: report of the ILAE Commission on Classification and Terminology, 2005-2009. Epilepsia 51 (2010): 676-685.

17. Espinosa JCA, Pardo CM, Moreno CM, Vergara J, Hedmont D, Sobrino MFE. Demographic and social profile of epilepsy in a vulnerable low-income population in Bogotá, Colombia. Neurologia 31 (2016):528-534.

18. Allers K, Essue BM, Hackett ML, et al. The economic impact of epilepsy: a systematic review. BMC Neurology 15 (2015): 2-16.

19. Devilat M. Aspectos prácticos de costos de la epilepsia. Revista Chilena de Epilepsia 1 (2004): 1-7.

20. Shellhaas RA, Berg AT, Grinspan ZM, et al. Initial treatment for nonsyndromic early-life epilepsy: an unexpected consensus. Pediatric Neurology 75 (2017): 73-79.

21. Ruiz-García M, Sosa-de-Martinez C, González-Astiazarán A, et al. Clinical-etiological and therapeutic profile of 719 mexican epileptic children. Child's Nervous System 18 (2002): 593-598.

22. Weijenberg A, Brouwer OF, Callenbach PM. Levetiracetam monotherapy in children with epilepsy: a systematic review. CNS Drugs 29 (2015): 371-382.

23. Egunsola O, Choonara I, Sammons HM. Anti-epileptic drug utilisation in paediatrics: a systematic review. BMJ Paediatric Open 1 (2017): e000088.

24. Pellock JM, Carman WJ, Thyagarajan V, et al. Efficacy of antiepileptic drugs in adults predicts efficacy in children: a systematic review. Neurology 79 (2012): 1482-1489.

25. Pozo AAJ, Pozo LD. Tratamiento con medicamentos antiepilépticos en el niño. Revista Cubana de Pediatría 85 (2013): 497-516.

26. Fattore C, Boniver C, Capovilla G, et al. A multicenter, randomized, placebo-controlled trial of levetiracetam in children and adolescents with newly diagnosed absence epilepsy. Epilepsia 52 (2011): 802-809.

27. Auvin S, Chhun S, Berquin P, et al. Aggravation of absence seizure related to levetiracetam. European Journal of Paediatric Neurology 15 (2011): 508-511.

28. Coppola G, Auricchio G, Federico R, et al. Lamotrigine versus valproic acid as first-line monotherapy in newly diagnosed typical absence seizures: an open-label, randomized, parallel-group study. Epilepsia 45 (2004): 1049-1053.

29. Gotlib D, Ramaswamy R, Kurlander JE, et al. Valproic Acid in Women and Girls of Childbearing Age. Current Psychiatry Reports 19 (2017): 1-7.

30. McFarland R, Hudson G, Taylor RW, et al. Reversible valproate hepatotoxicity due to mutations in mitochondrial DNA polymerase gamma (POLG1). Archives of Disease in Childhood 93 (2008): 151-153.

31. Pronicka E, Weglewska-Jurkiewicz A, Pronicki M, et al. Drug-resistant epilepsia and fulminant valproate liver toxicity. Alpers-Huttenlocher syndrome in two children confirmed post mortem by identification of p.W748S mutation in POLG gene. Medical Science Monitor 17 (2011): CR203-CR209.

32. Sarangi SC, Kaur N, Tripathi M. Assessment of psychiatric and behavioral adverse effects of antiepileptic drugs monotherapy: Could they have a neuroendocrine correlation in persons with epilepsy?. Epilepsy & Behavior 100 (2019): 1-9.

33. Bertsche A, Neininger MP, Dahse AJ, et al. Initial anticonvulsant monotherapy in routine care of children and adolescents: levetiracetam fails more frequently than valproate and oxcarbazepine due to a lack of effectiveness. European Journal of Pediatrics 173 (2014): 87-92.

Citation: Diana Leticia Pérez-Lozano, Liliana Carmona-Aparicio, Marcos Torres-Vázquez, Silvestre García-de la Puente, Miriam Palma-Barona3, Perla Michelle Martínez, Tarsila Elizabeth Juárez-Zepeda, Elvia Coballase-Urrutia, Liliana Rivera-Espinosa, Hortencia Montesinos-Correa, Aristides III Sampieri, Matilde Ruíz-García. Direct Medical Costs in the Care of Pediatric Patients with Nonsyndromatic Epilepsy: Using Levetiracetam and Valproic Acid. Journal of Cancer Science and Clinical Therapeutics 8 (2024): 000-000. 8 (2024): 126-134.