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# Levetiracetam prescription profile in children younger than 4 years treated at a tertiary care hospital in Chile

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## ABSTRACT

***Introduction.*** Levetiracetam (LEV) is an antiepileptic drug approved by the Chilean Institute of Public Health as concomitant therapy for epileptic seizures in children older than 4 years of age. However, it is widely prescribed from the neonatal period, which makes it necessary to evaluate its off-label use.

***Objective.*** To determine the prescription-indication profile of LEV in the treatment of epileptic seizures in children younger than 4 years in a tertiary care hospital in southern Chile.

***Population and method.*** Observational, descriptive, and retrospective study. The medical records of patients who started treatment with LEV between 2014 and 2019 were reviewed, and data on sociodemographic, pharmacological, and clinical variables were collected. The analysis was based on the description of the profile of patients, prescriptions, follow-up, and safety.

***Results.*** A total of 68 patients were included: 40 (58.8%) were males, 49 (72.1%) were born at a gestational age ≥ 37 weeks. The main etiology of epilepsy was structural (35.3%); LEV was mostly used in children diagnosed with central nervous system malformation (17.6%), and monotherapy was the prevailing dosage (55.9%). LEV was used for focal seizures in 50% of cases. Five children (7.3%) had psychiatric disorders, classified as probable adverse drug reactions.

***Conclusion.*** LEV was used in children with various diagnoses, with a low rate of adverse events. The profile of drug use varied in the different age groups. Future studies are needed to identify effectiveness, especially in newborn infants and patients with refractory epilepsy.


***Keywords:*** *levetiracetam; review of drug use; drug use; newborn; infant.*

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## INTRODUCTION

Epileptic seizures in children are a common neurological disorder accounting for approximately 1% of pediatric emergencies.[1] It has been shown that nearly two-thirds of children with epilepsy manage to be seizure free for more than 3 to 5 years, and nearly half of all patients successfully stop taking antiepileptic drugs. Advances in neuroimaging and genetics have made it possible to classify seizures according to their etiology as structural, genetic, infectious, immune-mediated, metabolic, and unknown.[2,3] In the neonatal context, the overall incidence of seizures reported worldwide is 0.4 per 1000 live births; it ranges from 0.2 to 1 per 1000 preterm live births compared to 0.4 per 1000 term live births.[4]

In relation to its pharmacological treatment, there is limited support for the use of antiepileptic drugs (AEDs) in the neonatal period. Phenobarbital is the first-line of treatment and achieves complete resolution of neonatal seizures, with an efficacy varying between 33% and 77%; however, it is not free of adverse effects and interactions during childhood and adulthood, such as motor and cognitive impairment.[5–7] In relation to other epileptic seizures, such as symptomatic seizures, there is no consensus on when and which drug to use, nor the duration of treatment. Further studies on antiepileptic therapies with innovative mechanisms of action continue to be necessary, especially in the infant-neonatal group, to demonstrate their efficacy and reduce long-term adverse effects.

Levetiracetam (LEV) is a second-generation AED formally approved by the Chilean Institute of Public Health in 2004 for the treatment of partial-onset seizures with or without generalization in adults, adolescents, and children older than 4 years. LEV is currently used before this age in children with focal seizures and focal seizures that progress to bilateral tonic-clonic seizures, probably related to its broad safety margin, linear pharmacokinetic profile, and lower incidence of adverse drug reactions (ADRs) and interactions, compared to other AEDs.[8–11]

Its pharmacokinetic and pharmacodynamic characteristics include almost complete absorption after oral administration and a bioavailability close to 100%. Peak plasma concentrations occur within 1 hour and steady state concentrations are reached within 2 days. The pharmacokinetics of LEV are linear, dose-proportional, and time-independent; it has low protein binding (< 10%) and is not metabolized by the liver cytochrome P450 (CYP) system. The body clearance of LEV in children is 30% to 40% higher compared to adults and, therefore, it is recommended that children receive a daily maintenance dose per total body weight (20–60 mg/kg/day) divided into 2 doses.[10,11] The adequate profile of LEV, given its pharmacology, seems promising and would make it an "ideal" AED; however, it is still necessary to demonstrate its sustained effectiveness and safety over time.

In this context, and in view of the fact that there are no studies on the use of LEV in children younger than 4 years in Chile, establishing the way in which AEDs are being used in relation to their indication, dosage, modifications of pharmacological treatment, and the identification with causality analysis of ADRs marks the contribution of studying these patients for a better understanding of the use of LEV in this age group.

Consequently, the objective of this study was to determine the profile of LEV prescription-indication in the treatment of seizures in children younger than 4 years in a tertiary care hospital in Valdivia, Chile.

## POPULATION AND METHOD

This was an observational, descriptive, and retrospective study on LEV use in patients younger than 4 years seen at a regional referral hospital in southern Chile who started their treatment in the May 2014–December 2019 period. Follow-up was extended throughout that period until December 2020, i.e., 1 year after the last patient included in the study started their therapy.

The initial screening was made using the drug dispensing information system based on prescriptions issued by the hospital's Department of Pharmacy; then, medical records were reviewed. The records of all patients with an indication for LEV, either as inpatients or outpatients, were reviewed. Thus, the study population or universe was included. Patients in whom LEV was indicated, but was not used or for whom follow-up for more than 24 hours was not possible were excluded.

The main study variables were:

- Profile of drug use: age range, dosage, etiologies involved, associations with other AEDs, selection as first- or second-line of treatment, and reason for discontinuation. In order to have an approximation of treatment duration, we specified the months of therapy during which LEV use or discontinuation

during follow-up was observed.

- Safety profile: the causality of ADRs was assessed based on the World Health Organization's algorithm.[12] This is a structured, systematic, and harmonized assessment tool that allows to define the causality of an individual suspected ADR. It assesses the criteria of temporality, previous knowledge of the ADR, course, re-exposure, and ruling out non-pharmacological causes, establishing the categories of causality: certain, probable, possible, unlikely, conditional/unclassified, and unassessable/unclassifiable.

Seizures were defined according to International League Against Epilepsy (ILAE) criteria as focal, generalized (focal onset and generalized), and status epilepticus. The etiology was classified as metabolic, structural, genetic, infectious, and of unknown cause.

Data were exported from Excel spreadsheets (Microsoft® Excel, 2010) to the SPSS v.15.01 statistical software (SPSS, Inc.). The analysis was based on descriptive statistics using absolute and relative frequency distribution for qualitative variables (nominal and categorical).

This study was approved by the Scientific Ethics Committee of the Valdivia Health Service (Regulation 320, dated September 30th, 2021). Given that patient data were collected retrospectively from medical records and that the dissemination of results is anonymized, an informed consent waiver was requested and authorized. Data management and the study in general were conducted in accordance with the recommendations of the Declaration of Helsinki and the Belmont Report.

## RESULTS

A total of 74 patients aged 0 days to 4 years started treatment with LEV at our hospital during the study period. Six patients were excluded: death before receiving LEV (2); indication of LEV for an unconfirmed diagnosis of epilepsy which was then confirmed to be bacterial meningitis (1); and early referral, for which only a dose was given at hospital discharge (3). The analysis included 68 patients. Of these, 47 started treatment with LEV during their hospitalization and 21 started treatment during their outpatient follow-up at the Pediatric Neurology Polyclinic.

Of the 68 patients, 40 (58.8%) were males; there was a higher proportion of gestational age ≥ 37 weeks (49 [72.1%]); and 35 had been born via vaginal delivery (51.5%). The most common type of seizures were focal seizures (50%) and the most common etiology was structural (35.3%) (*Table 1*).

Most LEV indications were in patients with central nervous system malformations (N = 12, 17.6%), followed by those with hypoxic ischemic encephalopathy and idiopathic epilepsy, both with 16.2% (N = 11); among the cases of hypoxic ischemic encephalopathy, it is worth noting that 6 had West syndrome (*Figure 1*).

The most common age at treatment initiation (*Table 2*) was older than 12 months (38.2%) and younger than 1 month (29.4%). LEV was the first-line choice in 17 patients (25%) and the second-line of treatment in 37 (54.4%). Twenty newborn infants were treated with LEV. LEV was the first-line choice in only 5 newborn infants. LEV was the second-line of treatment in 11 cases (9/11 after phenobarbital) (*Figure 2*). A loading dose was given only in 6 patients (8.8%). The most common dose was 30 mg/kg to 35 mg/kg (38.2%). At initiation, treatment was preferably oral (70.6%) and, in most cases (55.9%), as monotherapy (*Table 3*).

In 19 patients (27.9%), treatment was discontinued due to the absence of seizures for over a year with normal electroencephalogram (EEG); in 11 patients (16.2%), discontinuation was not recorded because they were referred to another facility; in 7 patients (10.3%), due to lack of response; 7 patients (10.3%) died; and 5 had suspected ADR (7.3%), which led to drug discontinuation.

The duration of LEV treatment was over 24 months in 25 patients (36.8%). In patients who continued with their LEV treatment, it was associated with 2 or 3 AEDs, mostly in relation to an epileptic encephalopathy diagnosis. The doses of the 5 patients who developed an ADR varied: 40 mg/kg/day (3), 30 mg/kg/day (1), 20 mg/kg/day (1).

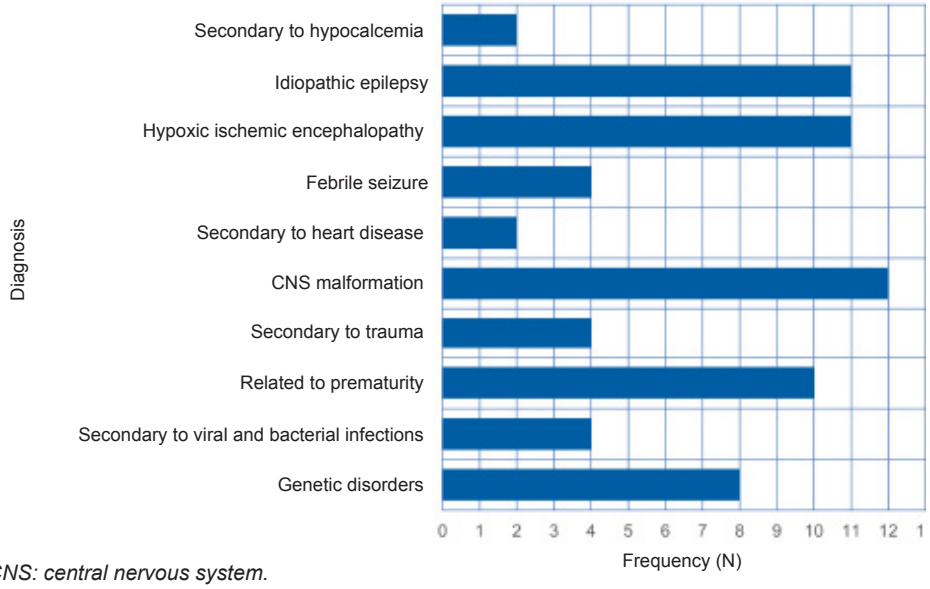
ADRs were classified as probable because they met the temporality criterion (between 6 and 15 months); all patients were receiving monotherapy and other potential causes were ruled out. In the 5 patients, the ADR was described as psychiatric disorder, which manifested as irritability, leading to LEV discontinuation and shifting to another AED. In the next follow-up visit of the 5 patients, which was conducted between 3 and 6 months later, irritability was no longer described in the clinical examination.

**Table 1. Characteristics of patients treated with levetiracetam (N = 68)**

| Variables | Frequency | | |
|---|---|---|---|
| | N | | % |
| Sex | | | |
| Male | 40 | | 58.8 |
| Female | 28 | | 41.2 |
| Weeks of gestation | | | |
| < 37 weeks | 19 | | 27.9 |
| ≥ 37 weeks | 49 | | 72.1 |
| Type of delivery | | | |
| C-section | 33 | | 48.5 |
| Vaginal | 35 | | 51.5 |
| Asphyxia | | | |
| Yes | 9 | | 13.2 |
| No | 59 | | 86.8 |
| Delayed psychomotor development | | | |
| Yes | 23 | | 33.8 |
| No | 45 | | 66.2 |
| Mechanical ventilation | | | |
| Yes | 21 | | 30.9 |
| No | 47 | | 69.1 |
| Type of seizure | | | |
| Status epilepticus | 7 | 10.3 | 10.3 |
| Focal seizure | 34 | 50.0 | 50.0 |
| Generalized seizure | 27 | 39.7 | 39.7 |
| Etiology | | | |
| Structural | 24 | 35.3 | 35.3 |
| Genetic | 20 | 29.4 | 29.4 |
| Infectious | 3 | 4.4 | 4.4 |
| Unknown | 7 | 10.3 | 10.3 |
| Unclassified* | 14 | 20.6 | 20.6 |

**Corresponding to neonatal seizure syndrome (N = 10) and febrile seizure (N = 4). N: number.*

**Figure 1. Distribution of patients treated with levetiracetam by indication**



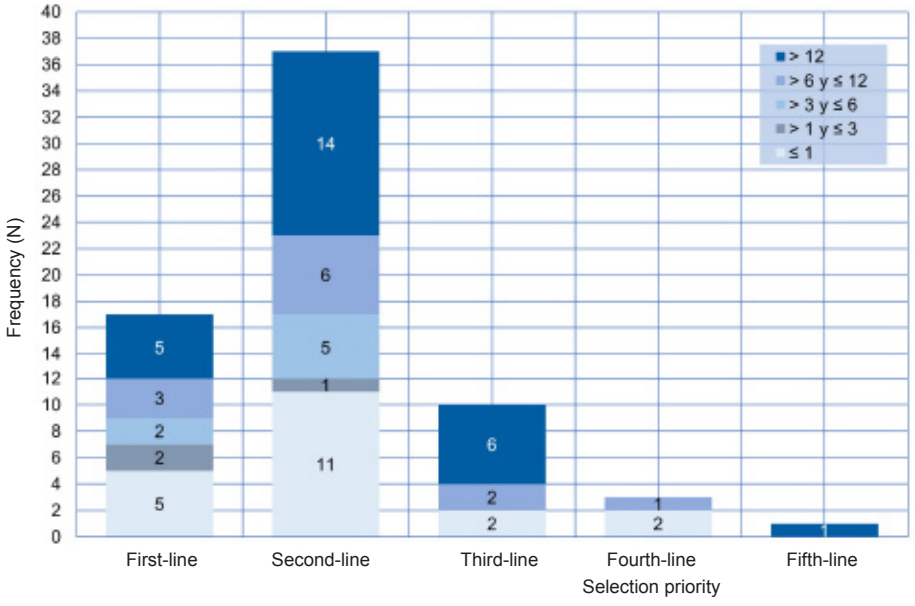

*N: number. CNS: central nervous system.*

**Table 2. Levetiracetam prescription**

| Criteria | Frequency | |
|---|---|---|
| | N | % |
| Age at initiation of LEV (months old) | | |
| ≤ 1 | 20 | 29.4 |
| > 1 to ≤ 3 | 3 | 4.4 |
| > 3 to ≤ 6 | 7 | 10.3 |
| > 6 to ≤ 12 | 12 | 17.6 |
| > 12 | 26 | 38.2 |
| Selection priority | | |
| First-line | 17 | 25 |
| Second-line | 37 | 54.4 |
| Third-line | 10 | 14.7 |
| Fourth-line | 3 | 4.4 |
| Fifth-line | 1 | 1.5 |
| Loading dose | | |
| Yes | 6 | 8.8 |
| No | 62 | 91.2 |
| Initial dose (mg/kg) | | |
| 20–25 | 10 | 14.8 |
| 30–35 | 26 | 38.2 |
| 40 | 20 | 29.4 |
| 50 | 9 | 13.2 |
| > 50 | 3 | 4.4 |
| Initial route of administration | | |
| Intravenous | 16 | 23.5 |
| Oral | 48 | 70.6 |
| Other (NGT, GT) | 4 | 5.9 |

*LEV: levetiracetam. NGT: nasogastric tube. GT: gastrostomy tube. N: number.*

**Figure 2. Selection priority and age at initiation of levetiracetam treatment**




*N: number.*

**Table 3. Characteristics of levetiracetam treatment**

| Dosage | Frequency | |
|---|---|---|
| | N | % |
| Monotherapy or not associated with other drug | 38 | 55.9 |
| Associated with 1 antiepileptic drug | 21 | 30.9 |
| Phenobarbital | 20 | 29.4 |
| Valproic acid | 1 | 1.5 |
| Associated with 2 antiepileptic drugs | 7 | 10.4 |
| Phenobarbital + midazolam | 1 | 1.5 |
| Clobazam + valproic acid | 1 | 1.5 |
| Phenobarbital + phenytoin | 1 | 1.5 |
| Clobazam + topiramate | 1 | 1.5 |
| Phenobarbital + valproic acid | 3 | 4.4 |
| Associated with 3 or more antiepileptic drugs | 2 | 2.8 |
| Phenobarbital + topiramate + phenytoin + vigabatrin + ACTH + valproic acid | 1 | 1.4 |
| Topiramate + vigabatrin + ACTH + valproic acid | 1 | 1.4 |
| Treatment duration (months) | | |
| 0–6 | 18 | 26.4 |
| 7–12 | 11 | 16.2 |
| 13–24 | 3 | 4.4 |
| > 24 | 25 | 36.8 |
| Unknown | 11 | 16.2 |
| Reason for discontinuation | | |
| No seizures | 19 | 27.9 |
| Normal EEG | 8 | 42.1 |
| 24 months | 4 | 21.0 |
| Unmet criteria (EEG/24 months) | 7 | 36.9 |
| Lack of response | 7 | 10.3 |
| Death | 7 | 10.3 |
| Adverse drug reaction | 5 | 7.3 |
| Ruled out diagnosis | 1 | 1.5 |
| Treatment withdrawal | 1 | 1.5 |
| Ongoing | 17 | 25.0 |
| Referral under treatment | 11 | 16.2 |

*ACTH: adrenocorticotropic hormone. EEG: electroencephalogram. N: number.*

## DISCUSSION

This study allowed establishing the use of LEV in children younger than 4 years in relation to the indication for which it was prescribed and other variables associated with its use in a health care center in southern Chile. LEV is registered by the regulatory agency of Chile for its use in children older than 4 years, although, in practice, it is also used in younger children. In this regard, international regulatory agencies (USA, Europe) have currently approved LEV as monotherapy for children from 1 month of age who have focal seizures. In our study, LEV was mostly prescribed in neonatal patients (29.4%) and older infants (38.2%), in line with what was reported by Le et al.,[13] who observed an increase in LEV use among neonates from 7.9% to 39.6% between 2007 and 2016. In addition, an increase in the use of LEV as first-line therapy for neonatal seizures from 11% in 2009 to 18% in 2018 has also been reported.[14]

In that study, LEV was mainly indicated as a second-line of treatment, which is consistent with reports in neonates, in which it is mostly used as second-line after phenobarbital (73.9%) and as first-line in only 17.4%.[15] In our study, LEV was the first-line of treatment in 25% of patients. The use of LEV as first-line by prescribers may be due to its safety profile, greater flexibility in plasma monitoring, and available dosage forms for an easy transition from intravenous to oral therapy that differentiates it from phenobarbital; this is in addition to the comparative advantages described, which include a low incidence of side effects and better neurodevelopmental outcomes.[16,17] In addition, in the study patients, 55.9% received LEV as monotherapy, similar to the 64% reported in neonates.[18] When not used as monotherapy, it was

mainly associated with phenobarbital.

In another scenario, in patients with status epilepticus, LEV was indicated in 7 patients as a second-line treatment, in accordance with current recommendations of benzodiazepine administration in children older than 1 month, and as second-line treatment with a LEV loading dose of between 20 mg/kg and 40 mg/kg intravenously.[19]

Associations with more than 3 AEDs with different mechanisms of action were observed in few patients in our study. A newborn infant with West syndrome was treated with LEV associated with 5 AEDs; LEV was selected as the third-line of treatment in high doses (70 mg/kg/day), with no adverse reactions. In the case of West syndrome, LEV is not routinely used as first-line, as it fails to reduce seizures; vigabatrin or adrenocorticotropic hormone (ACTH) are the treatment of choice.[20–22]

LEV has demonstrated a favorable and safe profile, with a low potential for drug interactions, a high bioavailability, and 30% to 40% higher clearance in children compared to adults. The recommendation is to start with an initial dose of 20 mg/kg/day divided into 2 doses, which are usually titrated up to a maximum of 40–60 mg/kg/day.[23] In our series, doses in this same range were used; the most commonly used doses were between 30 mg/kg/day and 35 mg/kg/day, and the maximum dose was 70 mg/kg/day in a patient who had central nervous system malformation, with no adverse reactions.

The data suggest that LEV may be effective for the treatment of neonatal seizures, with a favorable tolerability and adverse effect profile compared to phenobarbital (OR = 5.61, 95% CI: 2.53–12.44).[24]

A systematic review[25] described the most frequent behavioral effects in patients treated with LEV compared to other AEDs. Overall, the most common behavioral side effects reported were general behavioral problems (5.0%), irritability (4.2%), and hyperexcitability (3.4%), which led to LEV discontinuation. In our study, the rate of adverse effects of psychiatric disorder and irritability, which were reported spontaneously and led to LEV discontinuation, was greater than those described in the systematic review. In the causality analysis for LEV, the cases classified as probable were not re-exposed to the drug, and patients recovered once LEV was discontinued.[12] The safety of LEV is associated with good tolerability in children; however, further monitoring of short- and long-term effects is required to expand the use of LEV in the study group.[15,25]

Some limitations should be considered when assessing our findings:

- The limited number of patients studied, even though they corresponded to the study universe for the study period.
- Differential follow-up periods and lack of follow-up after a referral, which did not allow an accurate estimation of the duration of treatment, thus preventing the prediction of long-term outcomes and affecting the rational decision of which AED to use.[26]
- The clinical and EEG response to LEV was not analyzed; the lack of information and underreporting of the number of seizures does not allow to determine the effectiveness of LEV.

However, even with these limitations, the strength of this study is that it was the first to analyze the prescription profile of LEV in children younger than 4 years and, in addition, it studied its safety profile by applying the ADR causality algorithm.

To conclude, we defined the prescription profile of LEV: it was mostly indicated in children under 1 month of age and mainly in children diagnosed with central nervous system malformations. It was predominantly used as monotherapy for the control of focal seizures, with a low rate of ADRs. Further studies are required to establish the effectiveness and long-term adverse effects of this drug. ■

## REFERENCES


1. Mesa T, López I, Förster J, Carvajal M, et al. Consenso Chileno de Manejo de Fármacos Antiepilépticos en algunos Síndromes Electro-clínicos y otras Epilepsias en Niños y Adolescentes. *Rev Soc Psiquiatr Neurol Infanc Adolesc*. 2011;22(3):232-74.
2. Fine A, Wirrell EC. Seizures in Children. *Pediatr Rev*. 2020;41(7):321-47.
3. Yıldırım M, Bektaş Ö, Akıncı Göktaş Ö, Yüksel MF, et al. Levetiracetam monotherapy in children with epilepsy: Experience from a tertiary pediatric neurology center. *Epilepsy Behav*. 2021;116:107745.
4. Padiyar S, Nusairat L, Kadri A, Abu-Shaweesh J, Aly H. Neonatal seizures in the U.S. National Inpatient Population: Prevalence and outcomes. *Pediatr Neonatol*. 2020;61(3):300-5.
5. El-Dib M, Soul JS. The use of phenobarbital and other anti-seizure drugs in newborns. *Semin Fetal Neonatal Med*. 2017;22(5):321-7.
6. Arican P, Olgac Dundar N, Mete Atasever N, Akkaya Inal M, et al. Comparison of the neurocognitive outcomes in term infants treated with levetiracetam and phenobarbital monotherapy for neonatal clinical seizures. *Seizure*. 2020;80:71-4.
7. Karaoğlu P, Hız S, İşcan B, Polat AI, et al. Intravenous

Levetiracetam for Treatment of Seizures in Term and Preterm Neonates. *J Pediatr Neurosci*. 2020;15(1):15-20.
8. Contreras-García IJ, Cárdenas-Rodríguez N, Romo-Mancillas A, Bandala C, et al. Levetiracetam mechanisms of action: from molecules to systems. *Pharmaceuticals (Basel).* 2022;15(4):475.
9. Agrawal A, Banergee A. A review on pharmacokinetics of Levetiracetam in neonates. *Curr Drug Metab*. 2017;18(8):727-34.
10. Tan J, Paquette V, Levine M, Ensom MHH. Levetiracetam clinical pharmacokinetic monitoring in pediatric patients with epilepsy. *Clin Pharmacokinet.* 2017;56(11):1267-85.
11. Machado-Alba JE, Calvo-Torres LF, García-Betancur S, Aguirre-Novoa A, Bañol-Giraldo AM. Estudio de prescripción-indicación en pacientes que reciben antiepilépticos en Colombia. *Neurologia.* 2016;31(2):89-96.
12. World Health Organization. The use of the WHO-UMC system for standardised case causality assessment. 2013. [Accessed on: May 18th, 2022]. Available at: https://www.who.int/publications/m/item/WHO-causality-assessment
13. Le VT, Abdi HH, Sánchez PJ, Yossef L, et al. Neonatal antiepileptic medication treatment patterns: a decade of change. *Am J Perinatol*. 2021;38(5):469-76.
14. Sewell EK, Hamrick SEG, Patel RM, Bennett M, et al. Association between anti-seizure medication and outcomes in infants. *J Perinatol.* 2022;42(3):359-64.
15. Lloreda García JM, Fernández Fructuoso JR, Gómez Santos E, García-González A, Leante-Castellanos JL. Uso de Levetiracetam en crisis convulsivas neonatales. *An Pediatr (Barc).* 2017;86(5):286-8.
16. McHugh DC, Lancaster S, Manganas LN. A systematic review of the efficacy of Levetiracetam in neonatal seizures. *Neuropediatrics*. 2018;49(1):12-7.
17. Hooper RG, Ramaswamy VV, Wahid RM, Satodia P, Bhulani A. Levetiracetam as the first-line treatment for neonatal seizures: a systematic review and meta-analysis. *Dev Med Child Neurol*. 2021;63(11):1283-93.
18. Kanmaz S, Altun Köroğlu Ö, Terek D, Serin HM, et al. Efficacy of levetiracetam as first-line therapy for neonatal clinical seizures and neurodevelopmental outcome at 12 months of age. *Acta Neurol Belg*. 2021;121(6):1495-503.
19. Weijenberg A, Brouwer OF, Callenbach PM. Levetiracetam monotherapy in children with epilepsy: a systematic review. *CNS Drugs*. 2015;29(5):371-82.
20. Ramantani G, Ikonomidou C, Walter B, Rating D, Dinger J. Levetiracetam: safety and efficacy in neonatal seizures. *Eur J Paediatr Neurol*. 2011;15(1):1-7.
21. He Y, Tang J, Zhang M, Xiong T, et al. Efficacy of antiepileptic drugs in neonatal seizures: a systematic review protocol. *BMJ Paediatr Open*. 2020;4(1):e000683.
22. Pressler RM, Cilio MR, Mizrahi EM, Moshé SL, et al. The ILAE classification of seizures and the epilepsies: Modification for seizures in the neonate. Position paper by the ILAE Task Force on Neonatal Seizures. *Epilepsia*. 2021;62(3):615-28.
23. Obeid M, Pong AW. Efficacy and tolerability of high oral doses of levetiracetam in children with epilepsy. *Epilepsy Res*. 2010;91(1):101-5.
24. Qiao MY, Cui HT, Zhao LZ, Miao JK, Chen QX. Efficacy and safety of Levetiracetam vs. Phenobarbital for neonatal seizures: a systematic review and meta-analysis. *Front Neurol*. 2021;12:747745.
25. Halma E, de Louw AJ, Klinkenberg S, Aldenkamp AP, et al. Behavioral side-effects of levetiracetam in children with epilepsy: a systematic review. *Seizure.* 2014;23(9):685-91.
26. Liu BK, Jiang L, Li XJ, Hong SQ, et al. Efficacy and safety of levetiracetam in the off-label treatment of neonatal seizures. *Int J Neurosci*. 2020;130(4):336-42.